1990

Solid State Effects in the Reactions of the Meta and Pura Trifluorodiazomethane/Beta-Cyclodextrin Inclusion Complexes

Shelley Hunnings Smith
College of William & Mary - Arts & Sciences

SOLID STATE EFFECTS IN THE REACTIONS OF THE META AND PARA TRIFLUORODIAZOMETHANE/BETA-CYCLODEXTRIN INCLUSION COMPLEXES

A Thesis

Presented To

The Faculty of the Department of Chemistry

The College of William and Mary in Virginia

In Partial Fulfillment

of the Requirements for the Degree of

Master of Arts

by

Shelley H. Smith

1990

APPROVAL SHEET

This thesis is submitted in partial fulfillment of the requirements for the degree of

Master of Arts

Shelley H. Smith

Shelley H. Smith

Approved, August 1990

Christopher J. Abelt

Christopher J. Abelt, PhD.

Trevor B. Hill

Trevor B. Hill, PhD.

W. Gary Hollis, Jr.

Gary W. Hollis, Jr., PhD.

TABLE OF CONTENTS

ACKNOWLEDGMENTS

The author wishes to express her sincere appreciation to Professor Christopher J. Abelt under whose patient guidance and assistance this research was accomplished. It was an honor and a pleasure to work with him, an experience I will greatly value always. The author also wishes to thank the faculty members of the chemistry department for their continuous support and encouragement. The author is especially grateful to Professors Trevor B. Hill and Gary W. Hollis, Jr. for their careful reading and criticism of this manuscript.

LIST OF TABLES

LIST OF FIGURES

ABSTRACT

Relatively stable, solid complexes of beta-cyclodextrin with meta and para isomers of α, α, α-trifluorotoludiazomethane are made. Pyrolysis of the solid complexes produces carbene intermediates which undergo reactions with the beta-cyclodextrin hydroxyl groups. The insertion reactions are somewhat selective for the C3 hydroxyl, but the position of the trifluoromethyl group appears to have little effect on the regioselectivity. The size of the guest compound rather than the substituent location may determine the solid state structure which in turn determines the product distribution. Solid state inclusion effects differ dramatically from those previously observed in solution in terms of product selectivity.

SOLID STATE EFFECTS IN THE REACTIONS OF THE *META* AND *PARA* TRIFLUORODIAZOMETHANE/BETA-CYCLODEXTRIN INCLUSION COMPLEXES

Introduction

There exists a new focus in today's carbohydrate research upon a family of oligosaccharides known as cyclodextrins. Natural products formed by the degradation of starch, cyclodextrins can hardly be considered newly discovered compounds. The first isolation of cyclodextrin is recorded to have occurred in 1891.[1] Nonetheless, cyclodextrin research has peaked in only the last fifteen years.

The scope in which cyclodextrins are applied is vast. Industrial applications of cyclodextrins extend to the food, cosmetics, pharmaceutical, and agricultural industries. With increasing production, broadening research, and decreasing costs, a rapidly growing use of cyclodextrins is expected.

The growing interest in the use of cyclodextrins in the pharmaceutical industry is apparent in the number of papers and patents recently dedicated to cyclodextrins' medicinal applications. Through cyclodextrin inclusion complex formation, modifications of a drug's physical and chemical properties are possible. Some advantageous results of these complexations are masking of bad smell and taste, stabilization of volatile compounds, mixing of otherwise incompatible compounds, protection against oxidation and UV-degradation, increased

solubility, and reduction of side effects.[2] Of these effects, the two most important have been enhancement of bioavailability by improving the solubility of water insoluble or slightly soluble drugs and stabilization against oxygen, decomposition, or hydrolysis.[3,4] From continuing studies, it is becoming more and more evident that the use of cyclodextrins for medicinal purposes is highly favorable. It means, too, that in the future several thousand tons of the cyclodextrin market may be consumed by the pharmaceutical industry.

Like the pharmaceutical industry, the food and cosmetics industries are discovering the beneficial applications of cyclodextrins. Major advantages in using cyclodextrin complexes in foods and cosmetics include protection of active ingredients against decomposition, elimination or reduction of undesirable tastes and odors, and simplification of production through reduced packing/storage costs and more economical processes. The main use of cyclodextrins in both food and cosmetics is for the enhancement of flavors and fragrances. A relatively simple process, the preparation of β-cyclodextrin complexes of food flavors and fragrances has already been realized on an industrial scale.[3,5] Currently, the application of cyclodextrins in food and cosmetic products is severely restricted. However, just as in the pharmaceutical industry, the use of cyclodextrins in these industries is sure to increase as its numerous potential applications are explored.

Just as drug molecules and food flavors can be complexed

with cycldextrins, so can pesticides. All three of the industrially produced cyclodextrins can be used in the formulation of pesticide complexes.[6] At this point, very few papers have appeared concerning the application of cyclodextrins in agriculture. However, this in no way reflects a limitation to their use. It has been predicted that in future years a rapid development in agricultural applications can be expected.

In research, interest lies in cyclodextrin's role as an enzyme mimic. Cyclodextrin is a well-constructed miniature of an enzyme in the sense that it has a hydrophobic cavity of appropriate size, which enables it to act as "host" to molecules which may be included in the cavity. One of the most significant targets of cyclodextrin research is the basic understanding of specific binding and catalysis of enzyme action.[7]

Natural enzymes catalyze biochemical reactions by binding one or two small molecules into an active site, with catalytic groups of the enzyme held nearby so as to interact effectively with the bound substrate molecules. Enzymes can select and bind one particular molecule among the many that are present in solution in a cell. The enzyme can then selectively catalyze a reaction in one section of the molecule, not necessarily the section most prone to simple chemical attack. This catalyzed reaction is normally under strong geometric control by the enzyme, so that products will be formed with particular spatial arrangements.[8]

Like enzymes, cyclodextrins have the ability to bind substrates into interior cavities. The cyclodextrin molecule selectively binds particular molecules according to their size, shape, and hydrophobic character. It may then selectively produce a single product by a catalyzed reaction within the complex.

The research in this paper focuses on the preparation and selective reactions of β-cyclodextrin inclusion complexes of a thermally reactive guest compound. Interest lies in the effects inclusion geometry produces upon the reaction selectivity of the complexes.

Background: Cyclodextrins

Cyclodextrins are composed of α-(1,4) linkages of a number of D(+)-glucopyranose units in a macrocyclic array. A Greek letter is used to denote the number of glucose units contained in the cyclodextrin: α- for 6, β- for 7, γ-for 8, and so on. Sometimes cyclodextrins are referred to as Schardinger dextrins, as it was Schardinger who make the first detailed description of their preparation and isolation.

When starch is treated with the amylase of Bacillus macerans, α-, β-, and γ-cyclodextrins together with small amounts of higher cyclodextrins are produced. Isolation of the higher cyclodextrins (homologues of 9-12 glucose units) is rare, making exact characterization of their structure extremely difficult. α-, β-, and γ-Cyclodextrins, however, present few isolation problems. One successful method of separation is by selective precipitation.

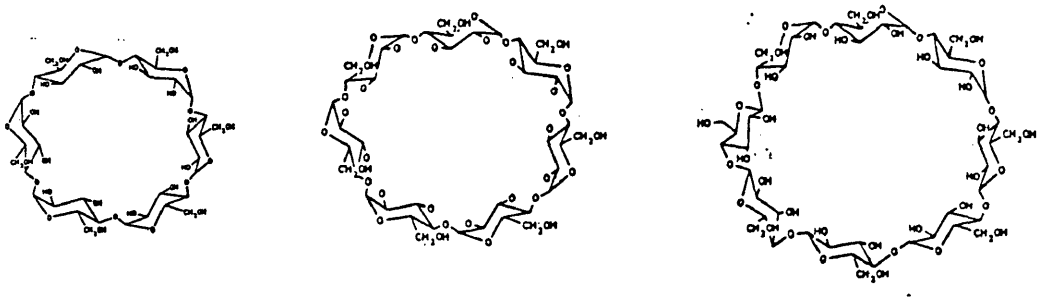


Fig. 1: Structures of α-, β-, and γ-cyclodextrins.

Structure

Cyclodextrins have torus shapes with all the glucose units in undistorted C1 (chair) conformations. The secondary hydroxyl groups (on the C2 and C3 atoms of the glucose units) are located on one side of the cone, whereas the primary hydroxyl groups are located on the opposite side of the cone. The inner cavity consists of a ring of C-H groups, a ring of glycosidic oxygens, and another ring of C-H groups. This structuring creates a relatively apolar interior in comparison to water.[9]

Cyclodextrin cavities are slightly "V" shaped with the secondary hydroxyl side being wider than the primary hydroxyl side. The primary hydroxyl groups are free to rotate, allowing them to partially block the cavity. The secondary hydroxyl groups, on the other hand, are on relatively rigid rings and, thus, cannot move very freely. These secondary hydroxyl groups are hydrogen bonded with the secondary hydroxyl groups of neighboring glucose units.[10,11]

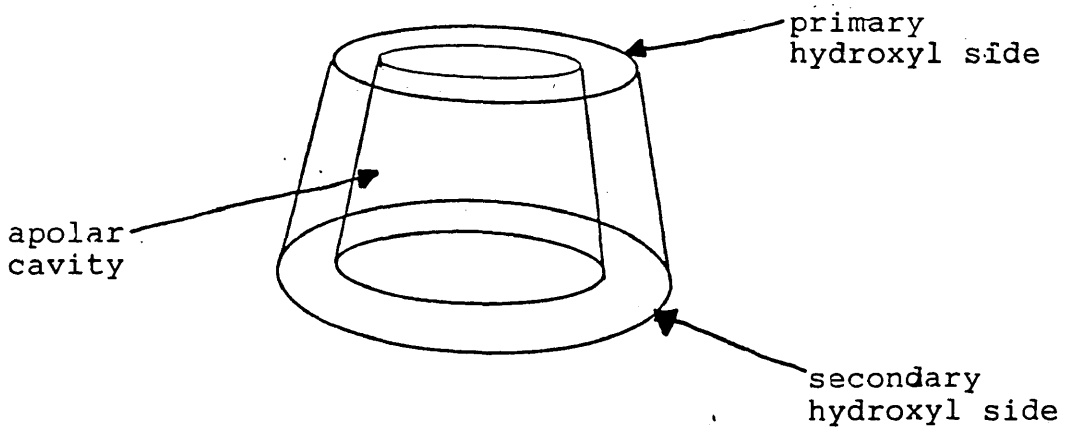


Fig. 2: The molecular shape of β-cyclodextrin.

In the crystalline state, cyclodextrin molecules are packed in one of two modes: cage or channel structure.[12,13] Cyclodextrin molecules are stacked on top of each other in channel structure. Cyclodextrins may align themselves "head-to-head" or "head-to-tail." In cage structure, cyclodextrin molecules are packed crosswise in one of two patterns: a herringbone pattern or a brick wall pattern. Due to these crosswise patterns, the cavity of one cyclodextrin molecule in this structure is blocked by adjacent cyclodextrin molecules.

Fig. 3: Channel, herringbone, and brick alignment of crystals.

The conformations of cyclodextrins in solution are quite important, since most of the reactions by cyclodextrins are carried out in solution, most ofter in water. In general, the conformations are nearly identical with those in the crystalline state. In aqueous solution, the cyclodextrin cavity is not an empty space. The cavities of cyclodextrin crystallized from water are filled with water molecules.[14] Cyclodextrin inclusion complexes are produced by substitution

of included water molecules by the appropriate guest molecule.

Inclusion Complexes

One of the most significant characteristics of cyclodextrins is the ability to form inclusion complexes with various compounds. Inclusion complexes are molecular compounds in which one compound (host molecule) spatially encloses another (guest molecule). In the case of cyclodextrin inclusion complexes, cyclodextrins act as host to a variety of guest compounds, ranging from polar reagents (acids, amines), small ions (ClO_4^-, SCN^-), and halogen anions[15] to highly apolar aliphatic and aromatic hydrocarbons.[16] The enclosed compound (guest molecule) is situated in the cavity of the host without significantly affecting the host framework structure. The size and shape of the cavity remain for the most part unaltered with the exception of a slight deformation. Inclusion complexes may be formed in solution or in the crystalline state. Water is the usual solvent, although inclusion complex formation may also take place in alternative solvents.[17]

There are several requirements which must be maintained to form a proper host-guest relationship. The binding sites of the host and guest molecules should be complementary stereoelectronically, for example.[18] In the host molecule, the binding sites are oriented in the same spatial direction. In the guest molecule, on the other hand, the binding sites

are diverging in the complex. It is this association of converging and diverging binding sites by which a host-guest complex is formed.

The tendency of certain substrates to complex with cyclodextrins can be correlated with the fit of the substrate to the cyclodextrin cavity.[19] Geometrical factors, rather than chemical, determine the species of guest molecule which will penetrate into the cavity. α-, β-, and γ-Cyclodextrins have different internal diameters and are thus able to accommodate molecules of different sizes. In a study of complex forming ability of α-, β-, and γ-cyclodextrins with cyclohexane, naphthalene, and anthracene,[20] data proved that all three cyclodextrins could include the cyclohexane molecule. Naphthalene was too large to fit in the α-cyclodextrin cavity. Only the cavity of γ-cyclodextrin could accommodate the bulky size of anthracene. Molecules of extremely small diameter are just as likely to encounter "fit" problems as those molecules of large diameter. Of Cl_2, Br_2, and I_2, Cl_2 is compatible only with α-cyclodextrin. The cavities of β- and γ-cyclodextrin are too large to ensure a proper fit. The molecule may pass in and out of these cavities with little apparent binding. I_2, possessing the largest diameter of these three diatomic molecules, is able to complex with all three homologues.

The orientation of included molecules in the host is usually arranged such that the maximum contact between

the hydrophobic part of the guest and the apolar cyclodextrin cavity is achieved. The hydrophilic part of the guest molecule remains at the outer face of the complex, ensuring maximum contact with both the solvent and the hydroxyl groups of the host. The success of complex formation may largely be determined by the polarity of the guest molecule. Only molecules which are less polar than water may be complexed by cyclodextrins. Strongly hydrophilic, hydrated, and ionized groups are only weakly complexable, if at all.[21] In addition, the stability of a complex is proportional to the hydrophobic character of substituents. To example, a methyl or ethyl substituent in the appropriate position will increase stability. A methyl group in a position ortho to a carbonyl group has a shielding effect on the hydrophilic carbonyl group, thereby increasing the hydrophobic character of the entire molecule. A similar substituent in the para position has a relatively weak effect.

The nature of the binding force of inclusion complexes is not fully understood. The interaction force is not believed to be a classical apolar binding such as that involved in enzyme-substrate complex formation. Inclusion complex formation is associated with a favorable enthalpy change and an unfavorable (or slightly favorable) entropy change, whereas apolar binding is usually characterized by a very favorable entropy change.[22]

Many proposals have been suggested to explain the favorable enthalpy change. Van der Waals interactions

and hydrogen bonding are among some of the effects which are credited. Guest-host van der Waals interactions in this case include both permanent dipole-induced dipole interactions[23] and London dispersion forces.[24] A phenomenon known as hydrophobic interaction is also thought to be a contributing effect in complex formation. In principle, water molecules from within a cyclodextrin cavity as well as those water molecules surrounding the guest compound must be removed before a guest can occupy the cavity. These water molecules join those water molecules in the surrounding water medium. An increase in the entropy of the system results.[25] Substitution by the guest transforms the energetically unfavorable conditions of the polar-apolar interaction of water molecules with the cavity to a more favorable interaction of the apolar guest with apolar host. The extent to which each of these driving effects contributes to the complex formation is dependent upon the nature of the guest molecule involved.

Preparation of Inclusion Complexes

Several methods have been developed for the preparation of cyclodextrin complexes. In principle, a solvent is not always necessary for complexation. A 1:1 β-cyclodextrin-salicylic acid complex has been synthesized by mixing both powdered crystalline compounds and storing in a closed bottle at ambient temperature for several months.[26] This

process is too slow to be practical. Complexation therefore is carried out in the presence of some solvent, most often water.

Complex formation in solution is a relatively simple and rapid process. Commonly, the guest (or a solution containing the guest) is stirred or shaken into an aqueous solution of cyclodextrin. Often the cyclodextrin solution is warmed to promote greater solubility. After a few hours, during which the mixture is continuously agitated and slowly cooled, an equilibrium is reached. Following the reaction, the mother liquor is removed by filtration. Experimental conditions such as temperature and reaction time will vary according to the nature of the guest compound and must be adjusted appropriately.

Another method of complex preparation is by suspension.[3,26] This method differs from the preparation described above in that the guest is stirred into an aqueous suspension of cyclodextrin rather than a solution. Complexation by this method may require a longer reaction time with durations of up to 24 hours. This technique is often preferred for use in industry.

Kneading is still another manner by which inclusion complexes may be formed.[3,26] A paste of cyclodextrin is prepared to which the guest is added. The grinding or kneading action applied to the past facilitates the inclusion of the guest. Since the cyclodextrin water complex (the original paste) is energetically less favored than

the inclusion complex to be formed, the reaction goes essentially to completion. Several hours grinding of the cyclodextrin+paste produces a powder-like complex.

Once an inclusion complex has been prepared, analysis is necessary to determine that the product formed is a true, homogeneous inclusion complex. The methods by which these analyses may be performed are numerous. There are thermoanalytical, spectroscopic, and chromatographic techniques available. Thin layer chromatography is one useful technique often employed. It is a simple test which can be performed with minimal time and cost expenditures. Verification of complex formation is determined by the R_f values measured for the guest compound and for the complex. R_f values for the complex should be lower than those for the pure guest.[27]

The most valuable method of verification is by nuclear magnetic resonance.[28] The principle behind the use of ^{1}H-NMR is that the hydrogen atoms located in the cavity interior, C3-H and C5-H, will be shielded by the guest if it is present in the cavity. Such effects will not be so evident with those hydrogen atoms, C2-H, C4-H, and C6-H, situated on the outer surface. Not only can the presence of the included guest be verified by the chemical shifts of the C3-H and C5-H atoms, but the position of the guest within the cavity can also be measured by the extent of these shifts.

In a study of complexes of β-cyclodextrin with substituted benzoic acids,[29] for example, the C3-H and C5-H atoms of the β-cyclodextrin demonstrated a large upfield shift upon the addition of benzoic acid. This upfield shift is credited to an anisotropic shielding effect of the benzene ring of the molecule. A complex of phenobarbital with β-cyclodextrin exhibited a small upfield shift of the C3-H atom and a large upfield shift of the C5-H atom. A shallower penetration of the benzene ring of phenobarbital would account for the smaller shift at the C3-H atom when compared to the shifts of benzoic acid.

Table 1: Chemical shifts of β-cyclodextrin complexes.

Substrate	Chemical Shift					
	H-1	H-2	H-3	H-4	H-5	H-6
Benzoic acid	+0.04	+0.04	+0.16	+0.03	+0.19	+0.05
p-Hydroxybenzoic	+0.04	+0.04	+0.14	+0.04	+0.21	+0.06
Phenobarbital	+0.04	+0.03	0.00	+0.06	+0.31	+0.11

^{13}C-NMR is a useful analytical tool as well. From ^{13}C-NMR spectra, it can be determined which atoms of the guest molecule are located inside the cavity and how these atoms are oriented. Higher shifts of guest carbon atoms are observed in complexes where there is a strong interaction between the wall of the cavity and the guest molecule. In a ^{13}C-NMR spectra of the inclusion complex of salicylic acid and heptakis-(2,6-di-O-methyl)-β-cyclodextrin, the

chemical shift difference of the carbon atom bearing the hydroxyl group is zero.[30] This measure indicates that this carbon atom of the guest is not included in the cavity, but rather must protrude from it.

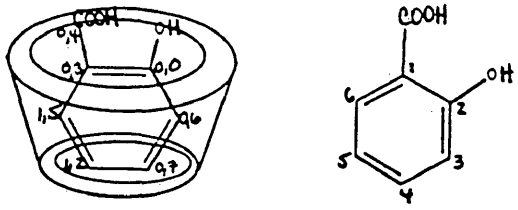


Fig. 4: Structure of salicylic acid-heptakis-(2,6-di-O-methyl)-β-cyclodextrin complex.

Cyclodextrin Substitution

Molecular models suggest that when a substrate such as anisole binds into the cavity of a cyclodextrin its ortho and meta positions would be shielded by the cyclodextrin. The para position however is accessible and may be substituted in an appropriate reaction.

Chlorination of aromatic compounds by hypochlorous (HOCl) showed that increasing cyclodextrin concentration results in increasing para/ortho ratios in the chlorinated anisole.[31] In the chlorination of anisole, para-chlorination occurred almost exclusively in the presence of cyclodextrin. In the absence of cyclodextrin, chlorination of the anisole occurred in a 60/40 para/ortho ratio. Kinetic studies

have shown that para-chlorination of cyclodextrin-complexed anisole is 5.6 times faster than that for the free anisole. Ortho-chlorination of the anisole complex, in the other hand, is almost completely hindered. Para-selectivity is due not only to the "naked bottom" structuring[32] but also by the proximity of the cyclodextrin-OCl group.

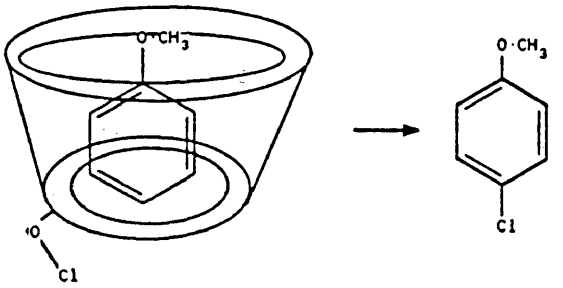


Fig. 5: Probable mechanism of selective p-chlorination of anisole.

Cyclodextrins as Enzyme Mimics

The ability of cyclodextrins and their derivatives to catalyze a number of chemical reactions has led to their description as enzyme models. Their catalytic properties have been described in terms of the formation of cyclodextrin-substrate inclusion complexes within the hydrophobic cavity and subsequent catalysis by either the hydroxy or other appropriate catalytic groups around the circumference of the cavity.[33]

A study by VanEtten, Sebastian, Clowes, and Bender[34] investigated the regioselective acceleration of phenol release from substituted phenyl acetates in the presence of cyclodextrin. Their data demonstrated that marked accel-

erations of the phenol release occurred as a result of addition of cyclodextrins to the reaction mixture. For example, m-t-butylphenyl acetate hydrolyzed 240 times more rapidly in the presence of 0.01 M β-cyclodextrin, and the hydrolysis of m-chlorophenyl acetate occurred 113 times more rapidly in the presence of 0.01 M α-cyclodextrin. In addition, a relationship was established between the regiochemistry of substitution of the phenyl acetates and the degree of acceleration of the hydrolysis reaction. Phenyl acetates having substituents in the position meta to the acetoxy group exhibited the largest rate accelerations. For example, m-t-butylphenyl acetate showed a 240-fold acceleration in the presence of β-cyclodextrin, whereas the para isomer showed only a 2.2 fold rate enhancement. The regioselectivity of the rate accelerations can be interpreted on the basis of an interaction of the secondary hydroxyl groups of the cyclodextrin (from carbon atoms 2 and 3 of the individual glucose residues). Kinetic studies proved that the large accelerations in the cleavage of meta-substituted phenyl esters in the presence of cyclodextrin are the result of a nucleophilic reaction of an alkoxide ion from the C-2 and C-3 secondary hydroxyl groups of the cyclodextrin.[35]

The importance of orientation of the catalytic site (the secondary hydroxyl group) around the reactive site (the carbonyl portion of the phenyl ester) inthe cleavages of phenyl esters was also indicated by comparing the effects of p-carboxyphenyl esters. β-Cyclodextrin showed a 5.3

fold acceleration in the cleavage of p-carboxyphenyl acetate.[36] However, in the cleavages of p-carboxyphenyl 2-methylpropionate and p-carboxyphenyl 3,3-dimethylbutyrate, which have more hydrophobic ester functions than the acetate, retardation was exhibited. Probably the hydrophobic ester functions of the substrates are included in the cyclodextrin cavity, since the hydrophilic carboxylate ion would not be readily included in the cavity because of its solvation requirement.[31] In these configurations of the inclusion complexes, the carbonyl carbon of the ester (the electrophile) is too far from the secondary hydroxyl group of the cyclodextrin (the nucleophile) for effective catalysis to occur. Acceleration by cyclodextrin in the cleavage of phenyl esters is thus attributed to the proximity effect between the catalytic and reactive sites.

Background: Carbenes

Organic chemists have long recognized the significant role of reactive intermediates in the synthesis of organic products. Many studies have focused upon the observation, characterization, and isolation of these intermediates. One such intermediate which has generated tremendous interest in recent years is the carbene. Carbenes, by definition, possess a divalent carbon.[37] The carbene carbon is linked to two adjacent groups by covalent bonds and, in addition, possesses two nonbonding electrons. A carbene may exist as a singlet or a triplet. If the two electrons are paired in the same orbital, then it exists in the singlet state. In the triplet state, the electrons fill different orbitals and have parallel spins.

singlet triplet

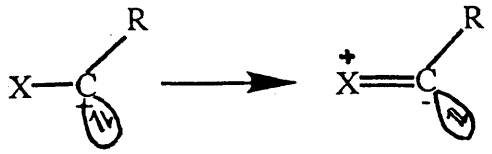
Fig. 6: Structures of singlet and triplet carbenes.

A carbene may exist in either state. The state in which it occurs depends upon the method by which the carbene

was generated.[38] As a result of these two different electronic configurations, different geometries and chemical reactivity should be observed.

From the diagrams, it is apparent that the carbene in the singlet state is $\underline{sp}^2$ hybridized, with the two electrons positioned in an $\underline{sp}^2$ hybridized orbital and an unoccupied p orbital remaining. Due to interorbital repulsions, the RCR angle is expected to be slightly less than the normal 120° angle.[32] The triplet carbene assumes $\underline{sp}$ hybridization and a linear geometry. Molecular-orbital calculations have predicted HCH angles in methylene (CH_2) to approximate 105° in the singlet state and 135° in the triplet state.[39] Experimental methods seem to confirm these predictions. By ESR the HCH angle has been measured to be 102°[40] and 125-140[41] for the singlet and triplet states, respectively. It is believed that the triplet state is the ground state, with an energy difference of 8 kcal/mole lower than the singlet.

Substituents affect the character of carbenes by altering the energies of the singlet and triplet states. Alkyl groups resemble hydrogen, thus generally dialkylcarbenes are ground state triplets.[42] Electronegative substituents, such as fluorine and oxygen, stabilize the singlet state.[43]



X=F, Cl, OR, NR_2

Fig. 7: Stabilization of carbene by electronegative substituents.

Carbene reactivity is strongly affected by substituent groups.[44] Singlet carbenes may be classified as ambiphilic, nucleophilic, and electrophilic based upon their reactivity toward a series of different compounds containing both nucleophilic and electrophilic alkenes. The principal structural feature which determines the reactivity of the carbene is the ability of the substituent to act as a π donor.

Generation of Carbenes

Carbene intermediates may be generated by numerous methods. One very general reaction is by decomposition of diazo compounds. Diazo compounds are not always easily synthesized, therefore this method may be limited by the success of a compound's preparation. Handling of the compounds must be carefully monitiored. Low molecular weight diazoalkanes are toxic and unstable. These compounds are usually prepared and used *in situ* rather than isolated.

Simple aliphatic diazo compounds are synthesized from derivatives of the corresponding amine. Base-catalyzed

decompositions involve two essential steps: (1) the initial substrate undergoes a base-catalyzed elimination and (2) is subsequently deprotonated at the α-carbon with the elimination of oxygen.[45]

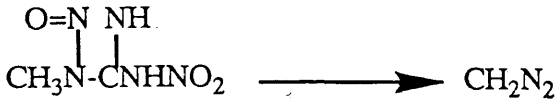


Fig. 8: Base-catalyzed decompostion of amine.

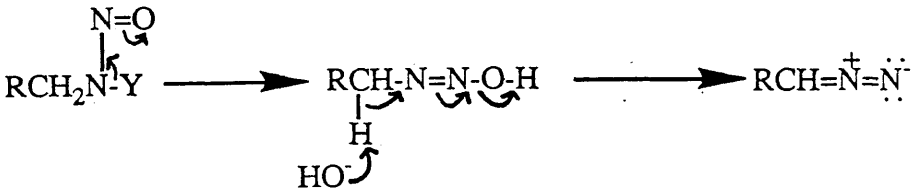


Fig. 9: Mechanism of base-catalyzed amine decomposition.

When one of the substituents is an aromatic group, the synthesis most often applied is the oxidation of the corresponding hydrazone.[46]

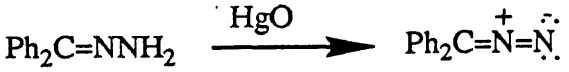


Fig. 10: Diazo synthesis through oxidation of the hydrazone.

The Bamford-Stevens reaction produces diazo compounds through a base-catalyzed thermal decomposition of p-toluenesulfonylhydrazones (tosylhydrazones) of aldehydes and ketones.[47] Diazo compounds are intermediates in these reaction schemes, resulting from the loss of p-toluenesulfinate from the tosylhydrazone derivative originally formed. Diazoalkanes can be prepared conveniently and in high purity by vacuum pyrolysis of dry sodium salts of tosylhydrazones. Frequently, the Bamford-Stevens reaction is used as a method in situ formation and decomposition of diazo compounds. The decomposition processes fall in two categories: (1) carbenic- in which nitrogen is expelled to give a divalent intermediate, or (2) cationic- in which a carbonium ion intermediate is formed by coordination with an electron-deficient reagent. The environment of the tosylhydrazone can affect the fate of the resulting diazo compound. Solvent choice can determine by which mechanism (carbenic or cationic) the diazo decomposes. In addition, compound structure can affect intermediate formation. Not all tosylhydrazones can be induced to give carbene intermediates. For example, tosylhydrazones of certain α,β-epoxyketones undergo a fragmentation reaction to yield an acetylene and a ketone.[41]

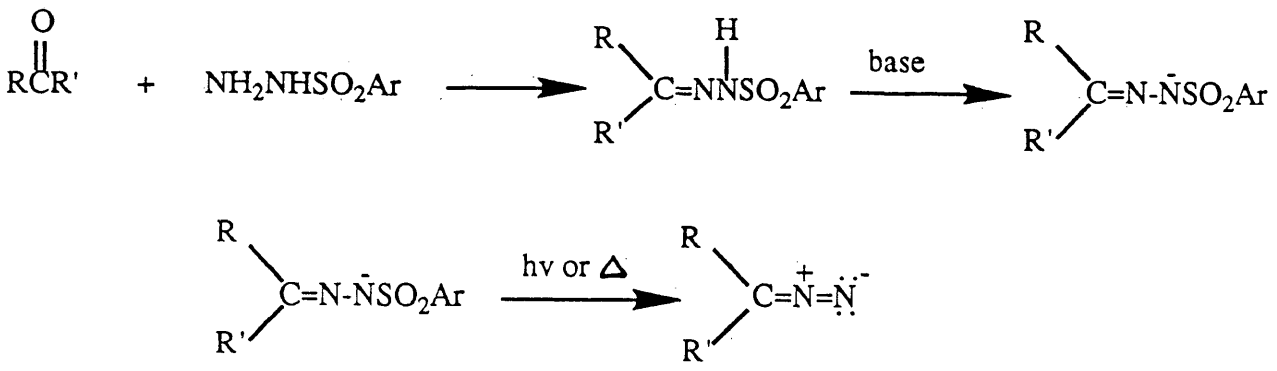


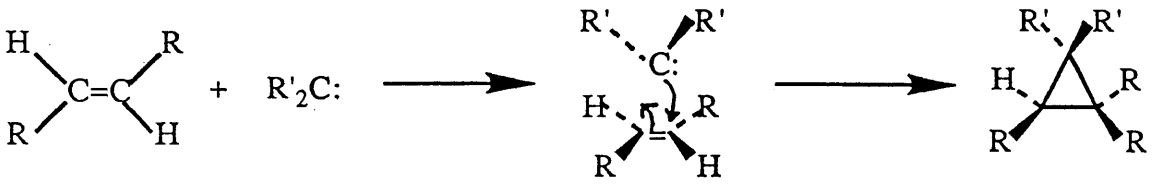
Fig. 11: Bamford-Stevens Reaction.

The driving force for decomposition of diazo compounds to carbenes is the formation of the very stable nitrogen molecule. Diazoalkanes in the gas phase possess activation energies of approximately 30 kcal/mole.[48] Photochemical excitation is one manner by which this energy may be supplied. Often the photochemical process may be controlled to yield predominantly singlet or triplet carbenes. Direct photolysis leads primarily to the singlet intermediate because the dissociation of the excited diazoalkene is faster than intersystem crossing to the triplet state. In photosensitized decomposition, the triplet carbene is the principal intermediate.[49]

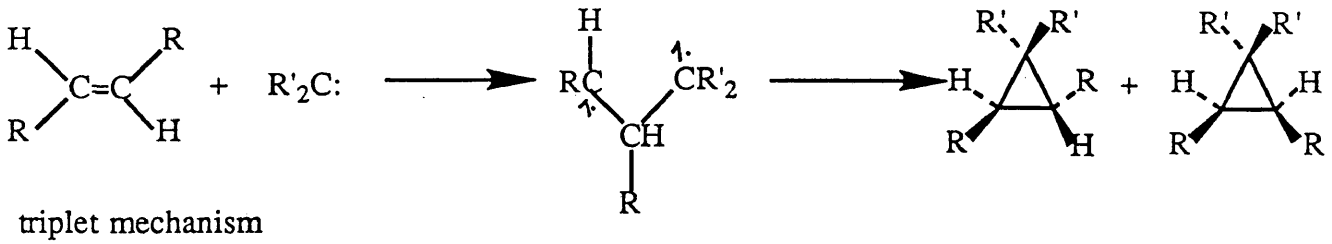
Carbene Reactions

For understanding carbene mechanisms and for synthetic applications, the addition reaction of carbene intermediates with alkenes has received the greatest attention. Reaction

of a singlet carbene or triplet carbene with an alkene usually produces a cyclopropane.[50] Singlet carbenes react via a one-step mechanism, thus retaining its stereochemistry in the cyclopropane. With the triplet carbene, an intermediate di-radical is involved. A spin inversion is required for the triplet state before further bond formation can occur. Since the rate of spin inversion is slower than the rotation about the single bonds, the cyclopropane formed from a triplet carbene will not necessarily have the same stereo-chemistry as the original alkene. Cyclopropanes formed from triplet carbenes usually result in a mixture of two stereoisomers.



singlet mechanism



triplet mechanism

Fig.12: Singlet and triplet carbene addition reactions.

Carbene addition is an exothermic reaction.[51] Two new σ bonds are formed and a π bond is broken in the process. These reactions are extremely rapid. The slow step

in carbene addition reactions under most circumstances is the generation of the carbene.

The Simmons-Smith reaction is a valuable method for converting alkenes to cyclopropanes. Methylene iodide and zinc-copper couple react to form a stable organozinc intermediate.[52]

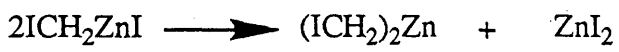


Fig. 13: Simmons-Smith reagent.

Transfer of a CH_2 unit occurs from the organometallic. Free $:CH_2$ does not act as an intermediate. The reaction exhibits stereospecific properties. In molecules with polar substituents (hydroxyl groups, in particular), the methylene unit is introduced onthe side of the double bond closest to the polar substituent.[53] Insertion reactions are processes in which a reactive intermediate inserts itself into an existing bond.[45] Carbene insertion reactions involving C-H Bonds can occur as a one-step process due to the high energy available to the carbene. As previously mentioned, these one-step processes may be performed only by singlet carbenes.

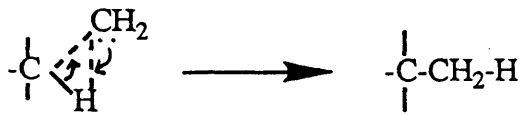


Fig. 14: Singlet methylene insertion into C-H bond.

Triplet carbenes may form similar products by a two-step mechanism involving H· abstraction and recombination.

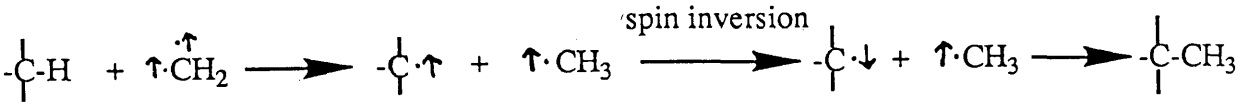


Fig. 15: Triplet carbene abstraction and recombination.

Oftentimes, difficulty arises in determining by which mechanism products were formed. Since the two electronic states exhibit stereochemical differences, the original carbene employed can be determined by evaluation of the stereochemistry of the products formed. Stereochemistry will be retained in the true one-step insertion reactions. In the two-step process of triplet carbenes, a loss of the original stereochemistry is anticipated since bond rotation may occur ahead of the spin inversion.[54]

Reaction of Monoaryl carbenes

In a study by Xavier Creary of the regioselectivity of singlet and triplet carbene addition reactions, a series of monoaryldiazomethanes was irradiated with 1,1-dimethyl-allene under direct irradiation and under benzophenone photosensitization.[55]

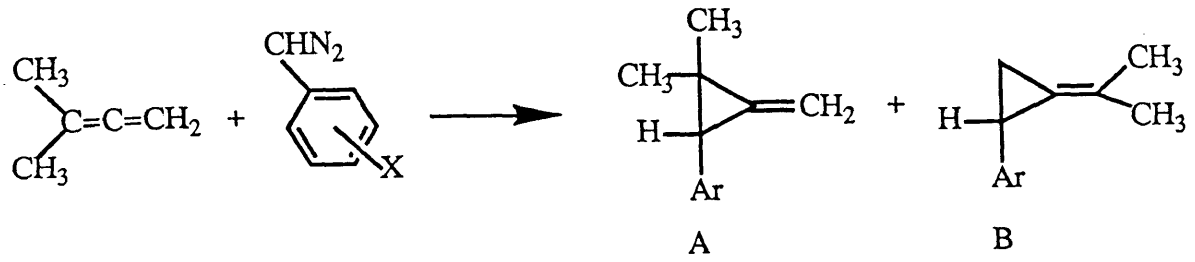


Fig. 16: Reaction of Aryldiazomethanes with 1,1-Dimethylallene.

In the direct irradiation experiments, the methylenecyclopropanes **A** were produced in larger amounts than the isopropylidenecyclopropanes **B**. However, the product ratio was found to be greatly substituent dependent. Electron-donating substituents such as p-methoxy, p-methyl, and p-fluoro lead to a much more regioselective reaction, while selectivity becomes quite low in the case of electronegative substituents. These results seem to indicate a greater singlet carbene stability in the case of more regioselective carbenes; the increased stability is attributed to delocalization. Likewise, carbenes such as **C** are destabilized (less selective) due to less favorable electronic interactions in the singlet.

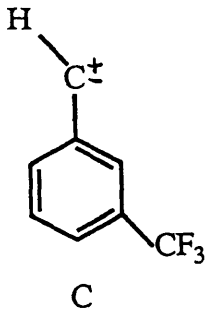


Fig. 17: Singlet Destabilizing Carbene.

The arylcarbene regioselectivity in addition to 1,1-dimethylallene indicates the ability of various substituents to stabilize singlet arylcarbenes. In the benzophenone-sensitized reactions, product ratios suggested that the products generated are predominantly derived from the singlet carbene. Since the ground states of many arylcarbenes have been suggested to be triplet[56], this would require a rapid triplet to singlet interconversion, with the singlet being more reactive with 1,1-dimethylallene than with the triplet. The electron donor substituents facilitate singlet formation. With singlet destablilizing substituents such as CF_3, increased amounts of triplet-derived **B** are formed from the initially generated triplet state. Even with these substituents, intersystem crossing to the singlet state occurs.

The Skell hypothesis[48] states that the singlets will add to olefins in a stereospecific fashion while triplet additions will be stepwise and give loss of stereospecificity. Creary's data is in agreement with this hypothesis. In addition, the data suggest that the solution chemistry of many monoarylcarbenes contains predominantly singlet character even when the triplet state is the initially generated state. With singlet stabilizing substituents, the degree of singlet involvement can be increased to the point where triplet reactions are unimportant. With electronegative substituents, increasing amounts of triplet chemistry can be seen. Electron-donor substituents stabilize the singlet state and hence increase selectivity.

Experimental Methods

General Methods: ^{1}H and ^{13}C NMR were recorded with a GE QE-300 spectrometer. Thin layer chromatography was carried out on 0.25 mm (60F- 254) precoated silica plates (Baker); spot detection was done by ultraviolet lamp and staining with vanillin solution. Flash-reverse phase chromatography was done with Baker RP-18 silica gel. Preparative HPLC was performed on a Waters 244 system equipped with a UV absorption detector (254 nm) using a Whatman Magnum 20 column packed with ODS-3. Analytical HPLC was performed on a Waters 600E system equipped with a variable wavelength absorption detector using a Whatman ODS-3 column. Melting points were taken on a Thomas Hoover capillary melting point apparatus and are uncorrected. α, α, α-Trifluorotolualdehyde (m and p) was purchased from Aldrich. β-Cyclodextrin was provided by Amaizo.

Synthesis of Diazo Compounds

α, α, α-Trifluorotolualdehyde p-toluenesulfonylhydrazone:

Meta isomer: A 2.88 g sample (0.015 mol) of p-toluenesulfonyl hydrazide was mixed with 10 ml 95% EtOH. As the slurry was swirled, 3.00 g (0.017 mol) of α, α,α-trifluoro-m-tolualdehyde was rapidly added. Within a few minutes, tosylhydrazone began to crystallize. After 15 minutes, the mixture was cooled in an ice bath. The product was collected on a Buchner funnel and washed with a small amount of ethanol.

Recrystallization afforded 1.73 g (5.05 mmol), 23% yield, m.p. 125.1-126.3°C) α, α, α-trifluoro-m-tolualdehyde p-toluenesulfonylhydrazone.

Para isomer: Procedure was identical to that for the meta isomer with the exception that 3.00 g (0.017 mol) of α, α, α-trifluoro-p-tolualdehyde was added to the slurry. The para isomer produced 4.33 g (12.65 mmol, 58% yield, m.p. 157.5-160.3°C) of α, α, α-trifluoro-p-tolualdehyde p-toluenesulfonylhydrazone.

α, α, α-Trifluorotolualdehyde tosylhydrazone sodium salt:

A 2.00 g (5.84 mmol) sample of the tosylhydrazone was dissolved in 10 ml MeOH. To the mixture, 10ml of 1 M methanolic NaOH was added. The solution was stoppered and left to stir for 15 minutes. The solvent was stoppered and left to stir for 15 minutes. The solvent was removed in vacuo, leaving the crude salt.

α, α, α-Trifluorotoludiazomethane:

The tosylate salt was subjected to vacuum pyrolysis (70-150°C, 90 min.) using an oil bath and an ice/acetone/liquid N_2 cooled receiver flask. Red-orange α, α, α-trifluorotoludiazomethane begins to collect at 90°C. Upon completion of the pyrolysis, 0.950 g (meta, 5.1 mmol, 47% yield) and 0.900 g (para, 4,8 mmol, 45% yield) of α, α,α trifluorotoludiazomethane was collected. Purity of the samples was determined by NMR. Trace amounts of azine

were present in the meta isomer. The para isomer appeared clean.

Inclusion Complex with Beta-cyclodextrin:

Complexation:

Meta Isomer: A solution of ∝, ∝, ∝-trifluoro-m-tolu-diazomethane (0.950 g, 5.1 mmol) in Et_2O (30 ml) was placed above a 0.04 M solution of -cyclodextrin (10.86 g, 9.6 mol) in H_2O (239 ml). The solutions were stirred together rapidly with a stream of N_2 directed over the Et_2O layer and with cooling in an ice bath. After 3 hours, the peach-colored solid was isolated by Buchner filtration and washed with deionized water. The solid was dried in vacuo and afforded 4.91 g of the complex (52% diazo incorporation). A sample of the complex was examined by ^{1}H-NMR. The NMR spectra indicated a guest/β-cyclodextrin host ratio of 0.7:1. The guest distribution (relative yield % based on integration of aromatic region) was 85 mol % diazo compound, 15 mol % other aromatic compounds.

Para Isomer: A solution of ∝, ∝, ∝-trifluoro-p-tolu-diazomethane (0.900 g, 4.8 mmol) in Et_2O (30 ml) was placed above a 0.04 M solution of β-cyclodextrin (10.86 g, 9.6 mol) in H_2O (239 ml). As in the method above, the solutions were stirred together rapidly. A stream of N_2 was placed above the Et_2O layer, and the entire mixture was cooled in an ice bath. After 3 hours, the peach colored solid

was filtered using a Buchner funnel and washed with deionized H_2O. A mass of the complex of 6.72 g was measured after drying in vacuo (81% diazo incorporation). An ^{1}H-NMR spectrum of a small sample of the complex was made. The NMR spectrum indicated a 0.7:1 guest/β-cyclodextrin host ratio.

Decomposition of α, α, α-Trifluorotoludiazomethane/β-CD:

The entire batch of complex was decomposed at 180°C for 10 minutes. A change of color from peach to white was observed. The pyrolysis products were cooled, dissolved in 350 ml H_2O, and extracted with 3x50 ml Et_2O. The aqueous layers were dried by rotary evaporation, yielding 2.81 g (meta) and 3.54 (para) of products.

Analysis of Aqueous Products:

Flash Reverse Phase Chromatography:

Small portions (ca. 1.00 g) of the water soluble products were ground finely through a copper sieve and mixed with 0.5 g of sea sand. The solid was subjected to flash reverse chromatography using the following gradient elution:

Table 2: Reverse Phase Gradient Elution

Fraction	% CH_3CN	Volume
1	1	250 ml
2	2	100
3	4	100
4	6	100
5	8	100
6	10	100
7	15	100
8	20	100
9	30	100
10	40	100
11	50	100
12	60	100

This process was repeated until the entire mass of derivatives had been used. The fractions were analyzed by thin layer chromatography. Those fractions containing the desired compounds were concentrated in vacuo, affording 502.4 mg product from the meta (15% yield) and 1482.4 mg (29% yield) from the para.

High Performance Liquid Chromatography:

Products from the flash column were further isolated and purified by preparative HPLC. A program elution sequence of 15% to 30% acetonitrile/water over 30 minutes was employed. Three peaks of interest were collected and dried in vacuo (meta- peak A: 102.3 mg, R_t=15.8 min., peak B: 35.8 mg, R_t=30.1 min., peak C: 36.4 mg, R_t=29.1 min.; para- peak A: 125.9 mg, R_t=12.4 min., peak B: 34.7 mg, R_t=24.8 min., peak C: 41.7 mg, R_t=27.5 min). Approximately 35% of the injected meta material and 17% of the injected para material was recovered. Each peak was verified by analytical HPLC (15%-25% acetonitrile/water elution gradient over 30 minutes).

Nuclear Magnetic Resonance:

The fractions were analyzed by ^{1}H- and ^{13}C-NMR. Meta: C3: ^{13}C-NMR: (DMSO-d_6, D_2O) 139.5, 134.5, 130.6, 130.3 (q, J=31.8 Hz), 126.7, 125.8, 123.5, 103.5, 103.2, 103.0, 102.3, 82.6, 82.5, 82.4, 79.4, 74.3, 74.2, 73.8, 73.6, 73.4, 73.1, 73.0, 61.0, 60.7 ^{1}H-NMR: (DMSO-d_6, D_2O) 7.67-7.82 (m, 4H), 5.12, (d, J=11.6 Hz, 1 Hz, 1 H), 5.00 (d,

J=11.6 Hz, 1H) and β-CD resonances.

C2: ^{13}C-NMR: (DMSO-d_6, D_2O) 139.8, 132.4, 130.1 (q, J=32.1 Hz), 130.0, 125.1, 124.9, 123.0, 102.5, 102.3, 100.6, 82.7, 82.0, 80.6, 73.5, 72.9, 72.8, 72.7, 72.6, 72.3, 60.4, 60.3 ^{1}H-NMR: (DMSO-d_6, D_2O) 7.79 (s, 1H), 7.58-7.73 (m, 2H), and β-CD resonances.

C6: ^{13}C-NMR: (DMSO-d_6, D_2O) 140.8, 132.3, 130.4, 130.1 (q, J=30.8 Hz), 125.1, 124.6, 123.4, 103.2, 102.8, 102.6, 83.0, 82.3, 82.2, 82.1, 74.0, 73.9, 73.0, 72.9, 72.2, 71.4, 70.0, 60.8, 60.7 ^{1}H-NMR: (DMSO-d_6, D_2O) 7.58-7.68 (m, 4H), 4.64 (d, J=12.6 Hz, 1H), 4.55 (d, J=12.6 Hz, 1H), and β-CD resonances.

Para: C3: ^{13}C-NMR: (DMSO-d_6, D_2O) 143.4, 128.7, 128.0 (q, J=31.5 Hz), 125.0, 122.7, 102.1, 101.9, 101.3, 81.7, 81.6, 81.3, 78.6, 73.3, 73.2, 72.7, 72.5, 72.2, 60.1 ^{1}H-NMR: (DMSO-d_6, D_2O) 7.70 (d, J=8.4 Hz, 2H), 7.64 (d, J=8.4 Hz, 2H), 5.01 (d, J=11.7 Hz, 1H), 4.94 (d, J=11.7 Hz, 1H), and β-CD resonances.

C2: ^{13}C-NMR: (DMSO-d_6, D_2O) 143.2, 129.1, 129.0 (q, J=32 Hz), 125.9, 123.1, 102.6, 102.4, 100.7, 82.7, 82.2, 82.1, 82.0, 80.6, 73.6, 73.5, 73.2, 73.0, 72.7, 72.6, 72.5, 72.4, 72.3, 60.5, 60.4 ^{1}H-NMR: (DMSO-d_6, D_2O) 7.72 (d, J=8.1 Hz, 2H), 7.62 (d, J=8.1 Hz, 2H), 5.01 (m, 1H), and β-CD resonances.

C6: ^{13}C-NMR: (DMSO-d_6, D_2O) 143.8, 128.2 (q, J=32.4 Hz), 128.0, 125.4, 122.8, 102.7, 102.2, 82.4, 82.0, 81.8, 73.4, 73.2, 72.5, 72.3, 71.6, 70.6, 69.4, 60.4, 60.3, 60.2, 60.1 ^{1}H-NMR: (DMSO-d_6, D_2O) 7.70 (d, J=8.2 Hz, 2H), 7.55 (d, J=8.2 Hz, 2H), 4.63 (d, J=12.9 Hz, 1H), 4.56 (d, J=12.9 Hz, 1H), and β-CD resonances.

Results and Discussion

The diazo compounds were generated by vacuum pyrolysis of the tosylhydrazone sodium salts. Attempts were made to prepare the diazo via pyrolysis in ethylene glycol; however, results proved to be unsuccessful. Azine was the prominent product by this method. The vacuum pyrolysis method was very advantageous for determining the yield and purity of the diazo compound since the compound itself was completely isolated. However, their isolation presented a disadvantage as well due to the potential danger of their toxicity and explosiveness.

Inclusion complexes of β-cyclodextrin with the diazo compounds were prepared by stirring an ether solution of the diazo compound over an aqueous β-cyclodextrin solution. The ether acted as a phase transfer catalyst for the system. In the absence of ether, little incorporation of guest would occur. The diazo compound itself would rearrange to form azine. A light stream of N_2 gas was directed above the stirring mixture. The solids isolated from the inclusion complex preparation were assumed to be inclusion complexes rather than coprecipitates based on literature precedent and on indirect evidence. For example, it was found that the solids still retained their guest species upon pyrolysis at 180°C.

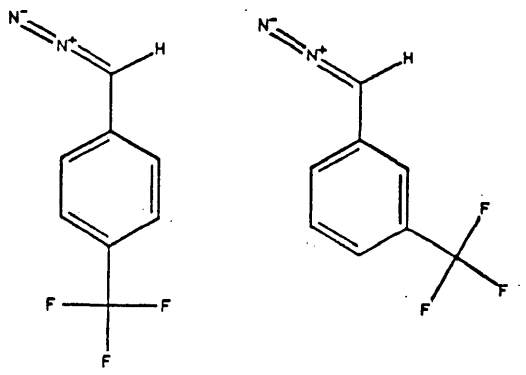


Fig. 18: Para and meta isomers of trifluorotoludiazomethane.

The extent of diazo incorporation was measured by NMR analysis. A small sample of the complex was dissolved in DMSO-d_6, which breaks up the complex into free cyclodextrin and free diazo compound. A ^{1}H-NMR spectrum was recorded. Guests-to-host ratios could be determined from the ratio of integrated intensities of the signals for aromatic and anomeric protons.

Table 3: Diazo inclusion ratios

Diazo Compound	Yield Based on Diazo	Guests-to-Host Ratio
meta	52%	0.7:1
para	81%	0.7:1

The diazo compounds of the complexes were decomposed by pyrolysis at 180-200°C. Under these conditions, carbenes should rapidly form upon elimination of N_2. Within 10 minutes, the complexes had lost their coloring- evidence of the carbene reaction.

Once formed, the carbenes may rearrange, react with other guest species, or react with the β-cyclodextrin. By

extraction, products resulting from carbene rearrangement or reaction with other species were separated from the products formed by reaction with β-cyclodextrin. The water-soluble β-cyclodextrin derivatives were easily isolated from those other products which remained in the ether layer. Derivatives bearing aromatic groups were separated from β-cyclodextrin using flash reverse phase chromatography. Isomers were separated by preparative reverse phase HPLC. Based on ^{1}H-NMR and ^{13}C-NMR data, the products were identified as O-H insertion products. Insertion can occur into one of three different hydroxyl groups (C2-OH, C3-OH, and C6-OH) in β-cyclodextrin, making three regioisomers possible. Pyrolysis of the inclusion complexes of this experiment produced all three insertion products.

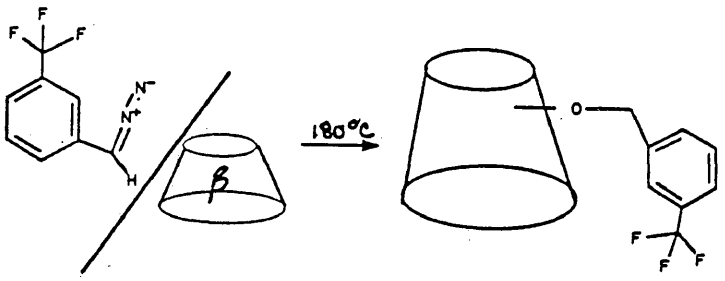


Fig. 19: H_2O-soluble pyrolysis products of the meta complex.

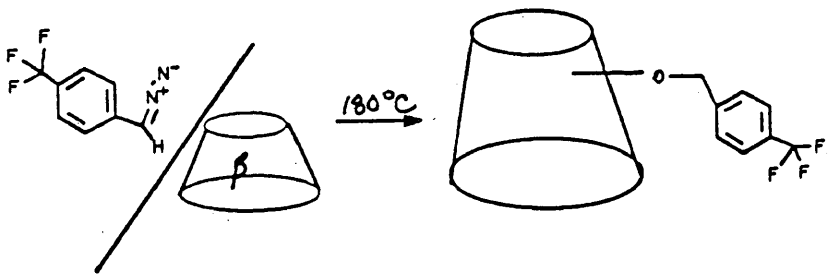


Fig. 20: H_2O-soluble pyrolysis products of the para complex.

^{13}C-NMR can identify the isomers separated by HPLC. Previous experimentation with β-cyclodextrin derivatives has shown that C6 derivatives show two resonances between 67 and 71 ppm.[57] Etherification of the C6-OH shifts the resonance of C-6 downfield by 8 ppm and shifts the C-5 upfield by 2 ppm. Fraction C of the meta and para complexes were thus identified as C6 derivatives. Further support of this conclusion is evident in the HPLC retention time of the fraction. Of the three fractions, C had the longest retention time.

The assignment of the C2 and C3 derivatives were more difficult. C2 derivatives show large shifts for C-1 and small shifts for C-4; C3 derivatives show the opposite trend. According to these distinctions, fractions A of the meta and para complexes are C3 derivatives and fractions B are C2 derivatives. Analytical HPLC chromatograms of the crude water-soluble β-cyclodextrin derivatives prior to separation by preparative HPLC showed the relative percent ratio of the three derivatives for each complex.

Table 4: Ratio of derivatives

Fraction	Relative Area%	Mass Isolated	Relative Mass%
Meta: A	40	102.3 mg	59
B	35	35.8	20
C	25	36.4	21
Para: A	58	125.9	62
B	22	34.7	17
C	20	41.7	21

The ratios of derivatives of both the meta and para complexes indicate that C-3 insertion products are strongly

favored over C2 and C6 products. Similar experimental results have been determined for α, α, α-trifluoro-o-toludiazomethane-β-cyclodextrin, as well. It is also evident from the data that the position of the substituent CF_3 group (o, m, or p) has little effect on the distribution of the three possible derivatives. The C3 insertion product accounted for approximately 60% of the synthesized derivatives of the o, m, and p isomers. C2 and C6 derivatives also were similar in their proportions, each accounting for approximately 20% of the products in each isomer's case.

These results should be compared to data previously established for other substituted diazomethane-β-cyclodextrin inclusion complexes: diazo(phenyl)methane-β-cyclodextrin, 1-diazo-1-phenylehane-β-cyclodextrin, diazo(diphenyl)methane-β-cyclodextrin, 1-naphthal-diazomethane-β-cyclodextrin, and 2-naphthal-diazomethane-β-cyclodextrin (see Table 5). In comparison, the trifluorotoludiazomethane-β-cyclodextrin complexes showed the greatest preference for C3 insertion. C6 insertion products were favored by the larger guests like the diazo(diphenyl)methane and the naphthaldiazomethanes.

Table 5: Distribution of Insertion Products

Diazo compound	C3	C2	C6
$PhCHN_2$	---76---		24
$PhMeCN_2$	18	23	59
Ph_2CN_2	0	36	64
o-CF_3PhCHN_2	60	8	32
m-CF_3PhCHN_2	59	21	20
p-CF_3PhCHN_2	62	17	21
1-$NaphCHN_2$	45	44	11
2-$NaphCHN_2$	19	0	81

From this data, some conclusions may be drawn concerning the solid state crystalline structures. Earlier crystallographic studies have determined that β-cyclodextrin complexes crystallize with a herringbone or channel structure.[57] The herringbone structure is favored when complexes involve guest compounds of relatively small molecular size. Complexes with larger guests, on the other hand, form channel structures.

The larger percentage of C3 insertion products in the inclusion complexes of the substituted aromatic diazo compounds (o-, m-, p-CF_3PhCHN_2 and $PhCHN_2$) indicates that these complexes possess a herringbone structure in the solid state. Inclusion complexes of the larger guest compounds (Ph_2CN_2, $PhCMeN_2$, and 2-$NaphCHN_2$) most likely form a channel structure. These inclusion complexes exhibited large proportions of C6 derivatives and minimal proportions of C3 derivatives. Such results are not surprising where the C3 is pointed away from the cavity, making it less accessible. With diazo(diphenyl)-methane-β-cyclodextrin, for example, the two phenyl groups will tend to align the divalent carbon along the center axis of β-cyclodextrin, hindering its scope for the reaction. Since the C2-OH and C6-OH are most accessible from inside the cavity, these are the expected sites of reaction.

Conclusion

The relatively stable, solid inclusion complexes of the meta and para isomers of α, α, α-trifluorotoludiazomethane-β-cyclodextrin were made. The complexes were thermally decomposed and extracted with ether to isolate the host-guest products. The regioselectivity of the products formed was examined by analysis by HPLC and NMR. The ratios of the C-2, C-3, and C-6 derivatives for the two isomeric complexes were determined and compared. C-3 insertion was preferred by both isomers. These results were compared with data previously collected for diazo compounds of different substituents. From these comparisons, conclusions may be made about solid state effects of inclusion complexes.

In solution, differences in substitution of a guest compound of a β-cyclodextrin inclusion complex will cause dramatic differences in the reactivity of the complex. In the solid state, however, substitution has little effect upon products. Of greater significance in the solid state is the size of the guest molecule which will dictate crystalline structure. Larger guests induce channel structuring, whereas smaller quests establish herribone formations. It is the solid state crystal structure which determines reaction products. Herringbone stuctures favor C3 insertion products as the C3-OH is so easily accessible. Channel structures favor C6 derivatives. Most likely this is due to the manner in which the guest aligns itself with the cyclodextrin cavity such that the C6-OH is accessible. The C3-OH in its orientation pointing away from the cavity is not so easily reached.

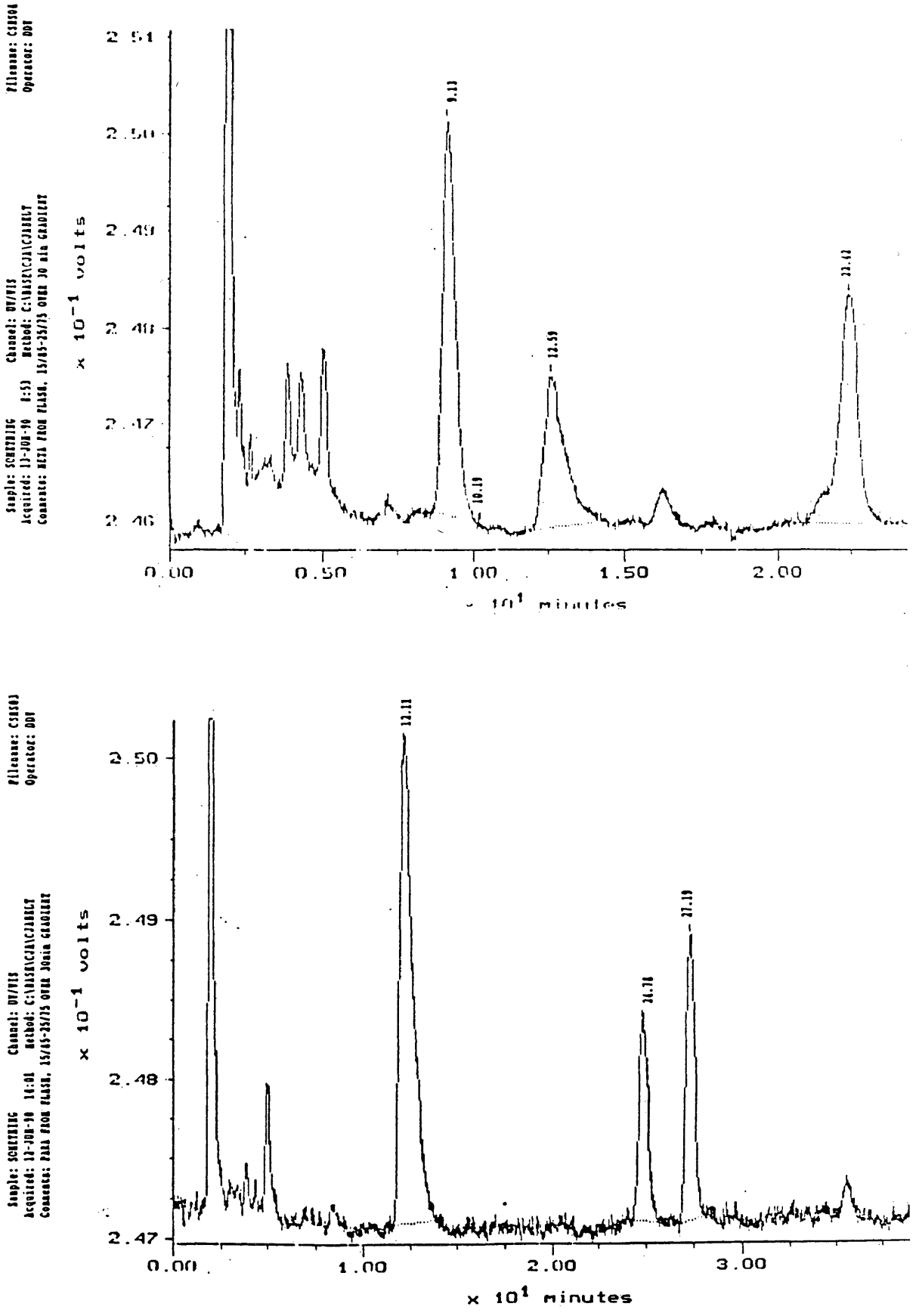


Fig. 21: Analytical HPLC chromatograms of meta and para complexes.

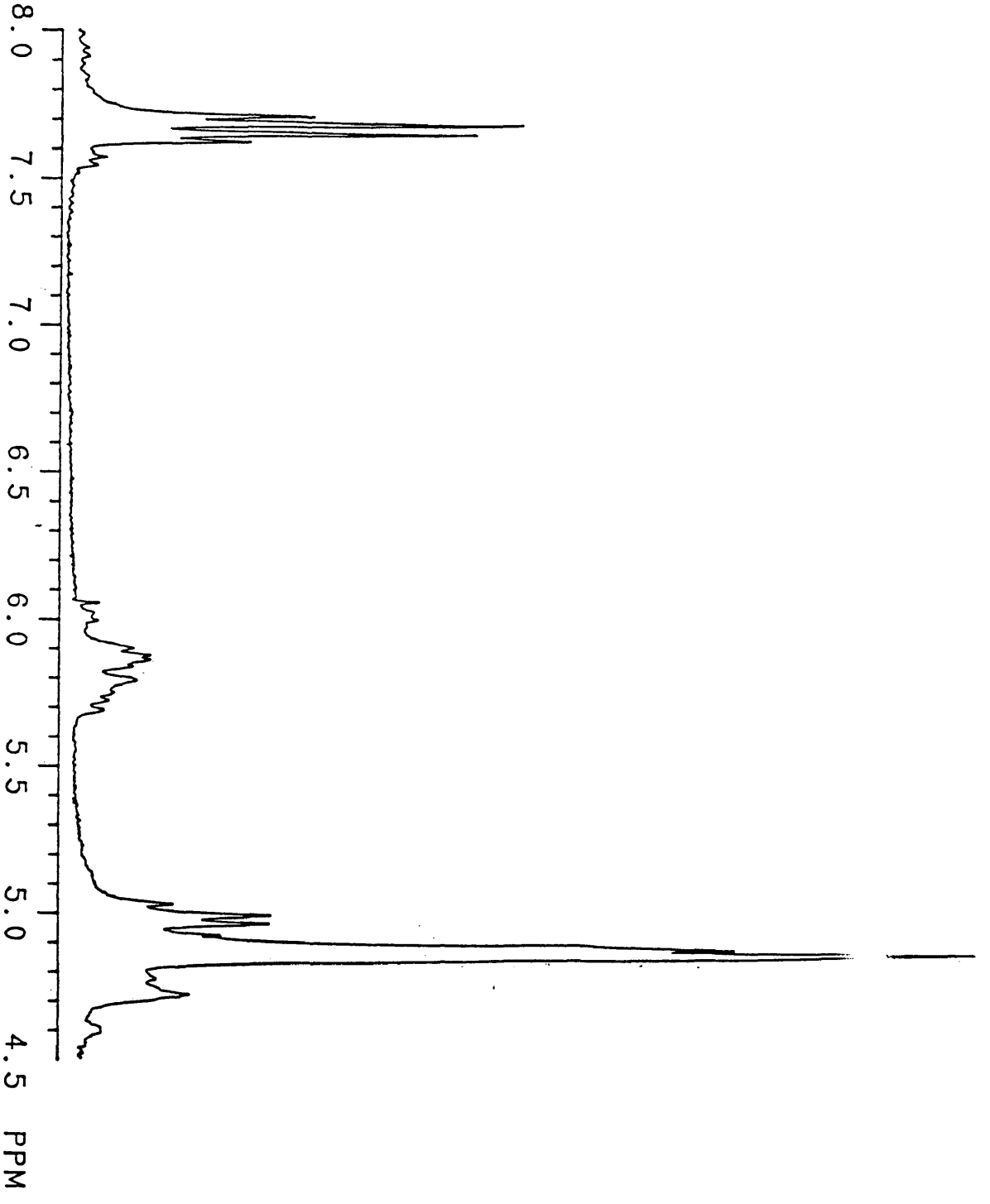


Fig. 22: ^{1}H NMR of para C3 insertion product.

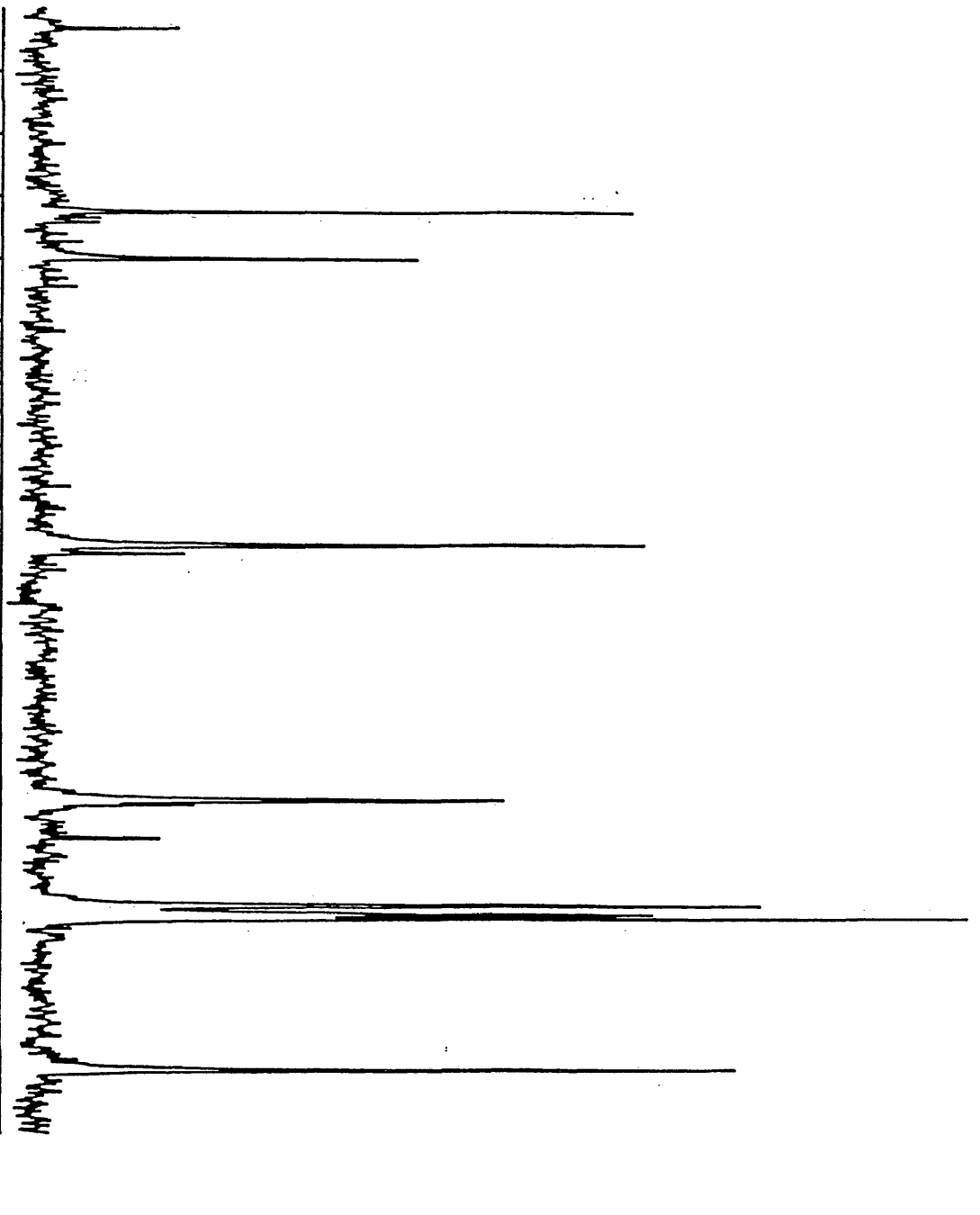


Fig. 23: ^{13}C NMR of para C3 insertion product.

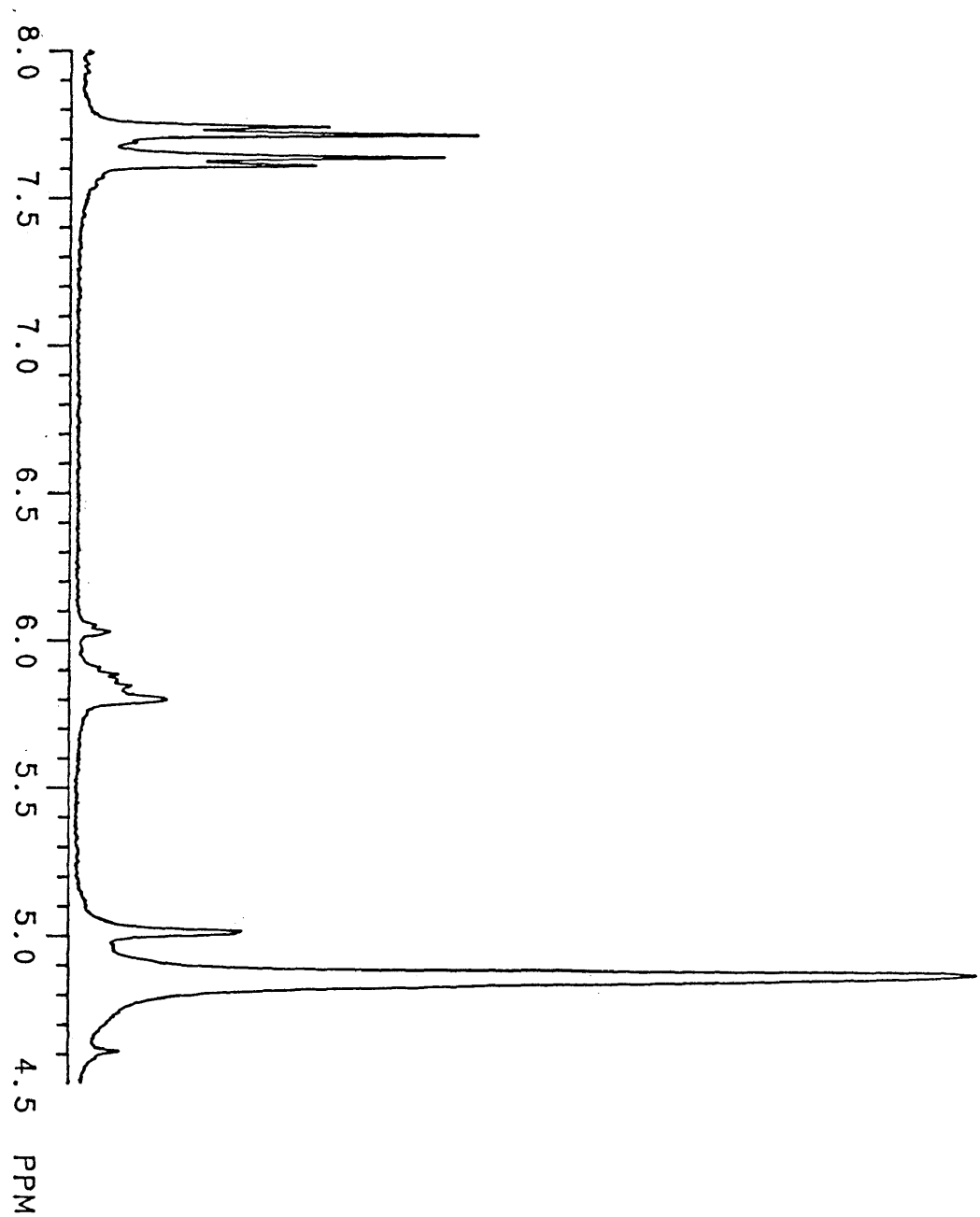


Fig. 24: ^{1}H NMR of para C2 insertion product.

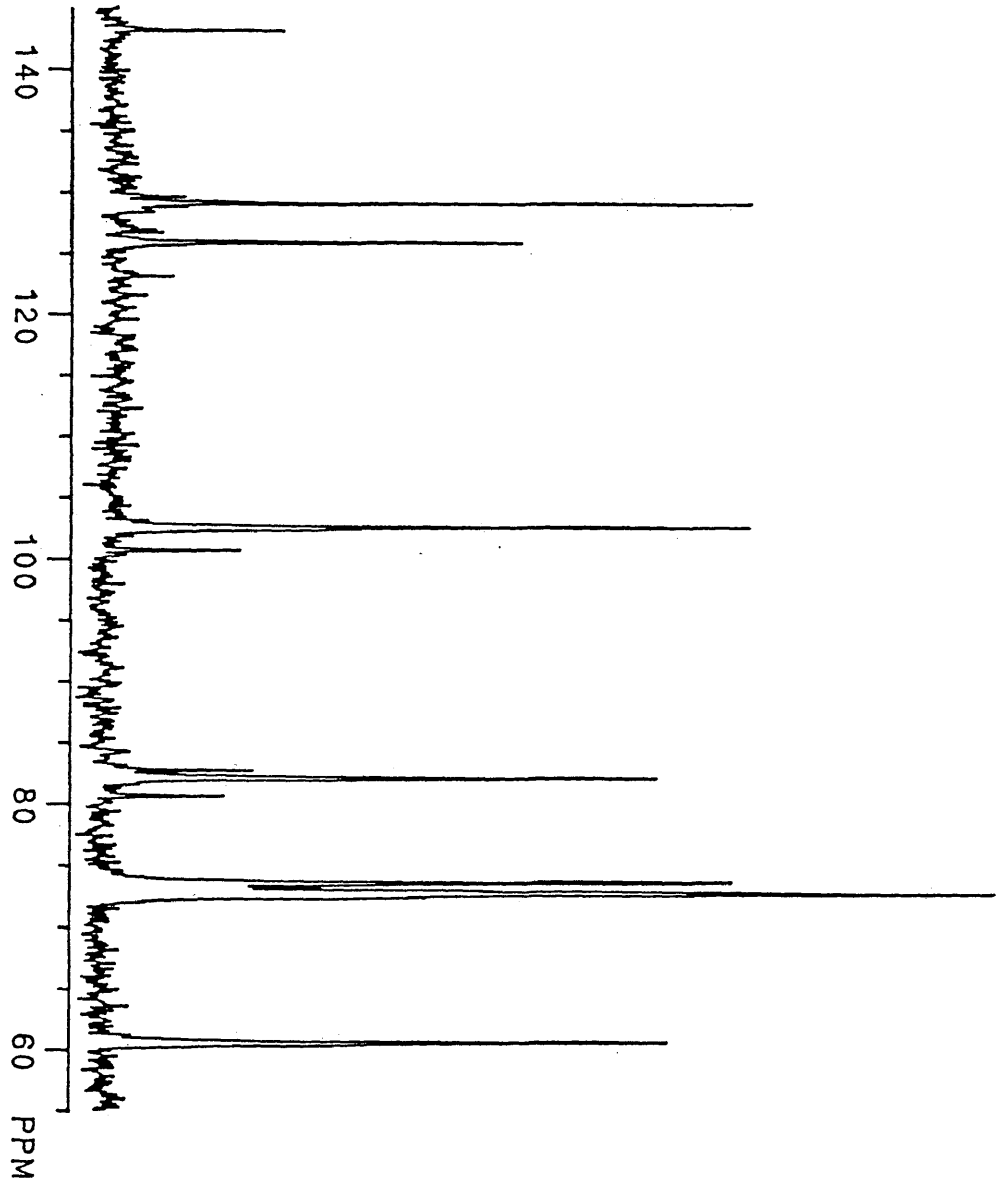


Fig. 25: ^{13}C NMR of *para* C2 insertion product.

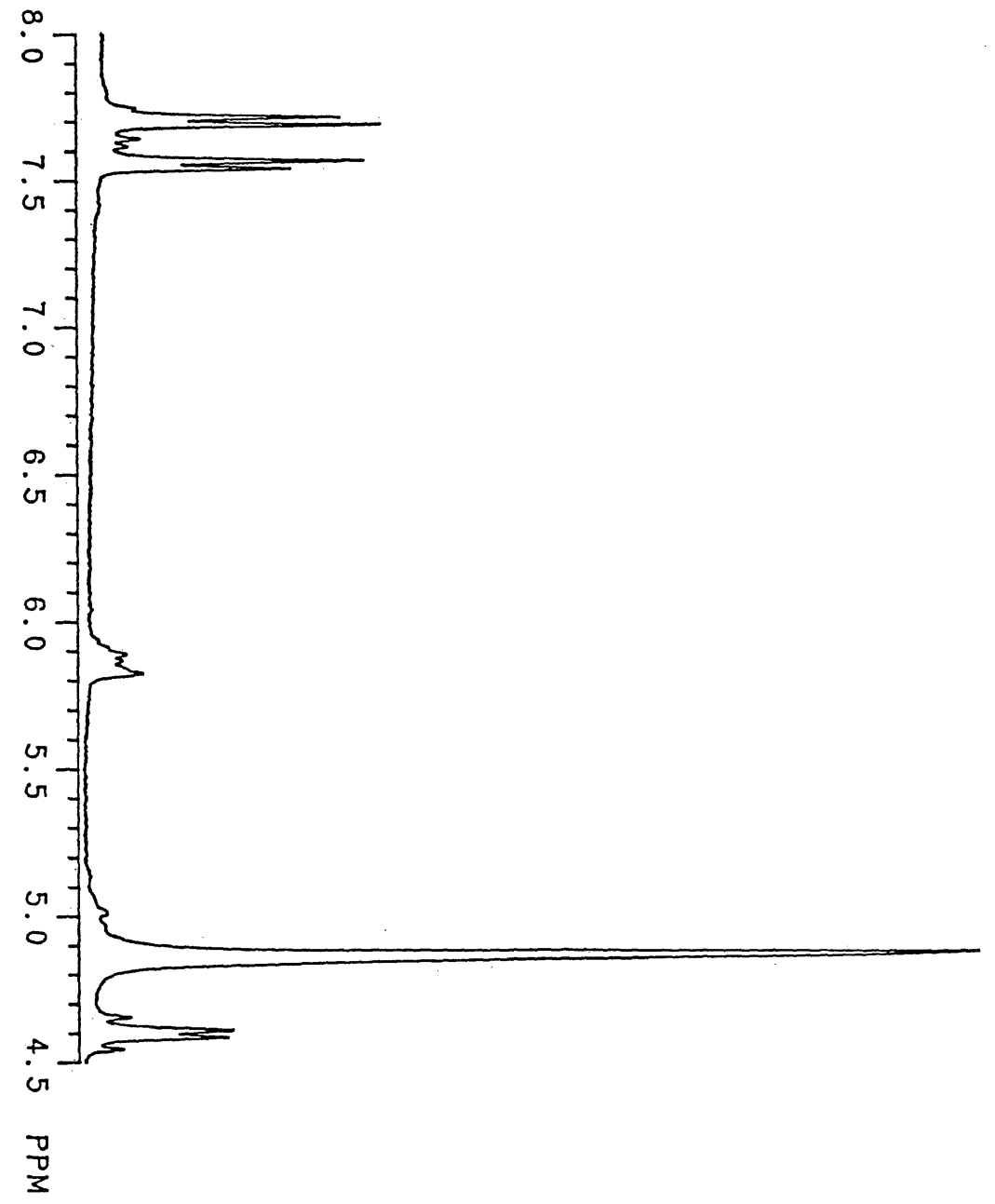


Fig. 26: ^{1}H NMR of *para* C6 insertion product.

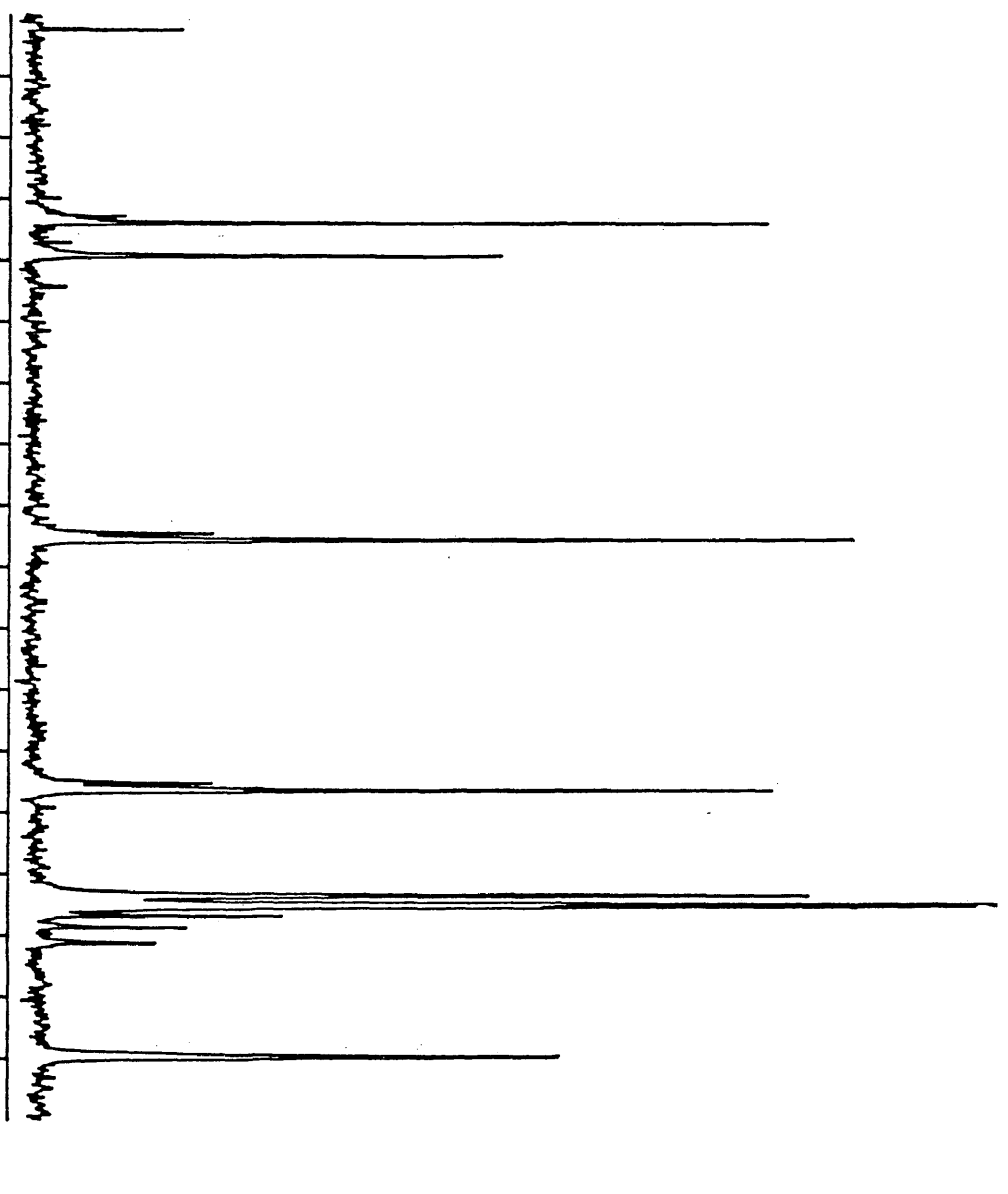


Fig. 27: ^{13}C NMR of para C6 insertion product.

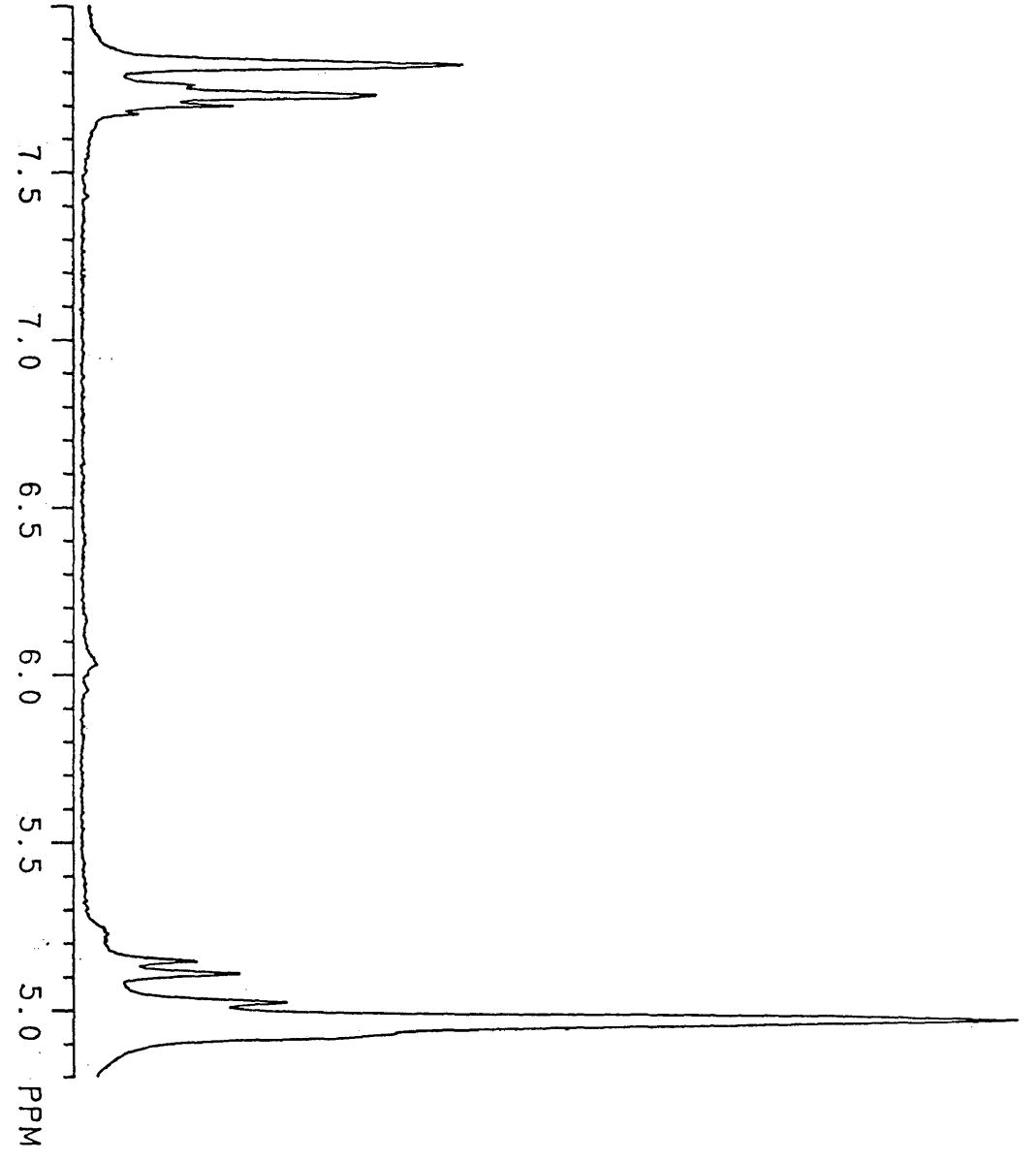


Fig. 28: ^{1}H NMR of meta C3 insertion product.

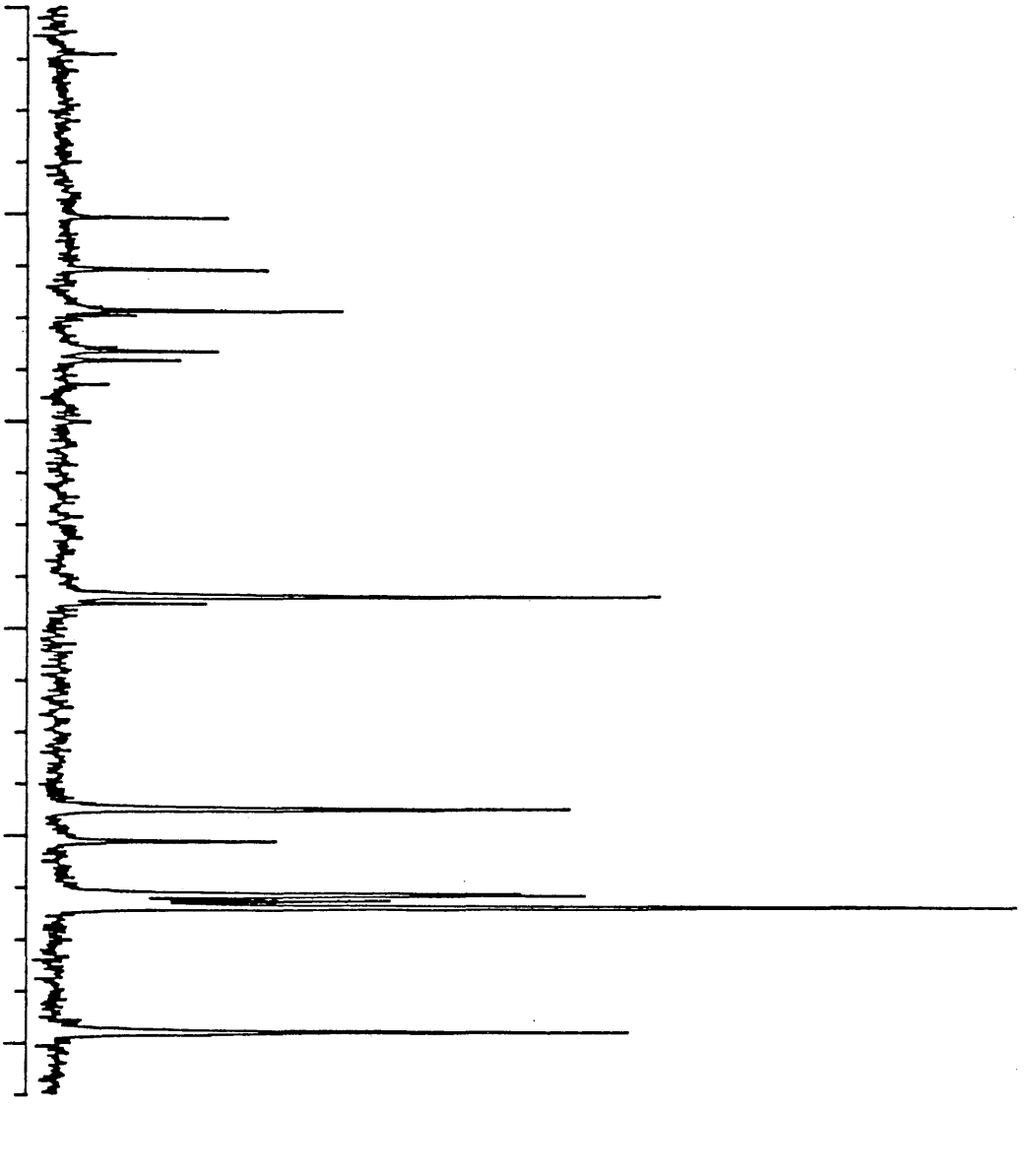


Fig. 29: ^{13}C NMR of meta C3 insertion product.

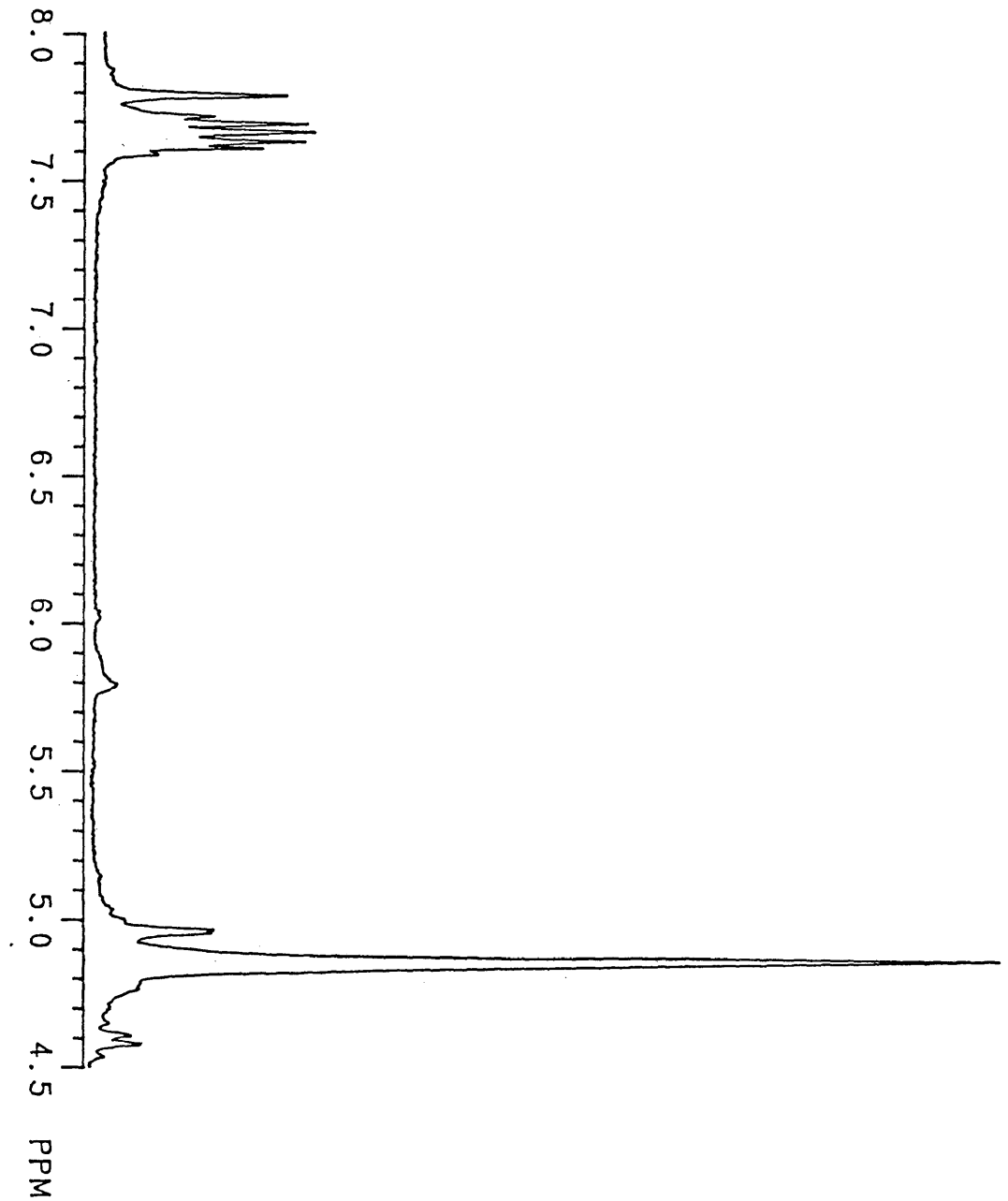


Fig. 30: ^{1}H NMR of meta C2 insertion product.

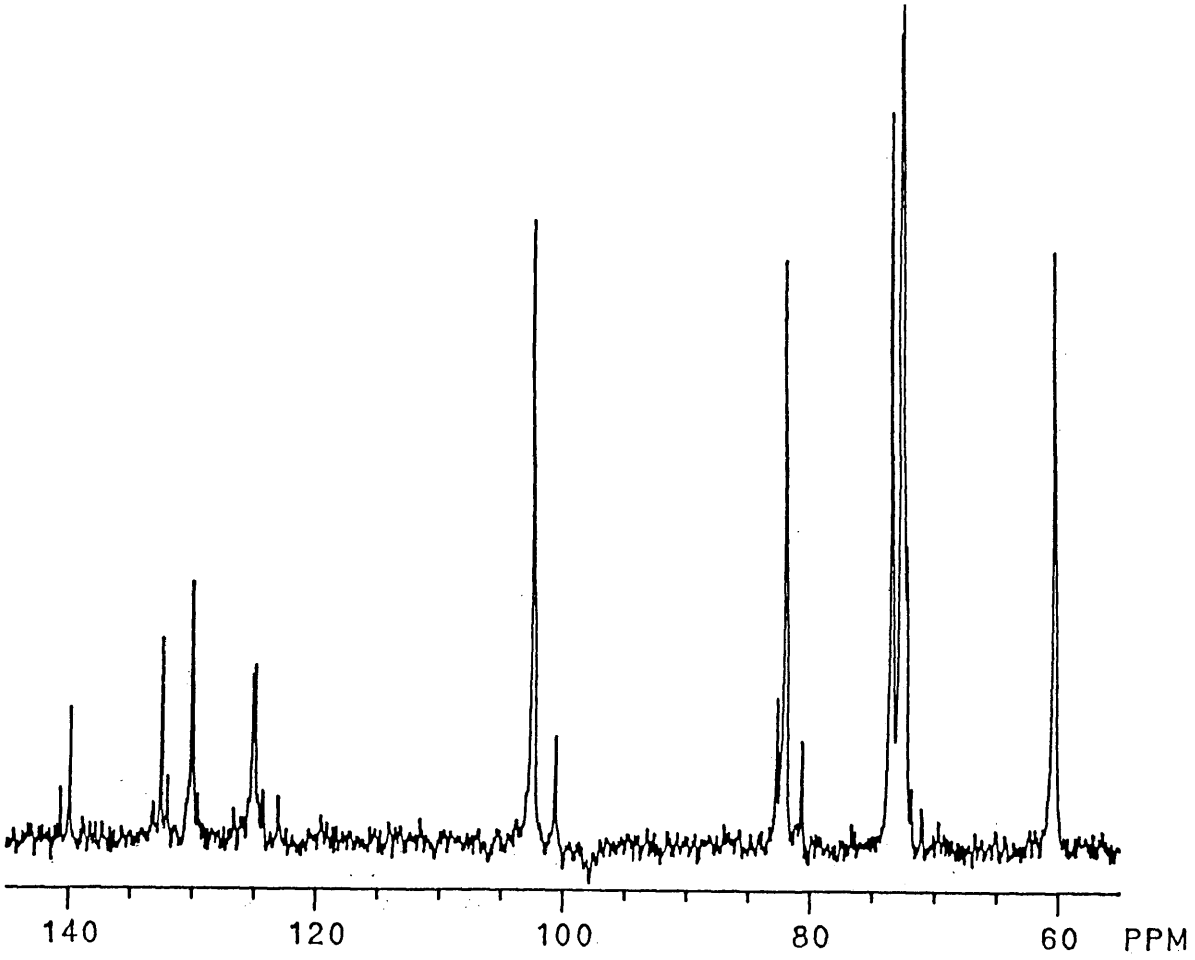


Fig. 31: ^{13}C NMR of meta C3 insertion product.

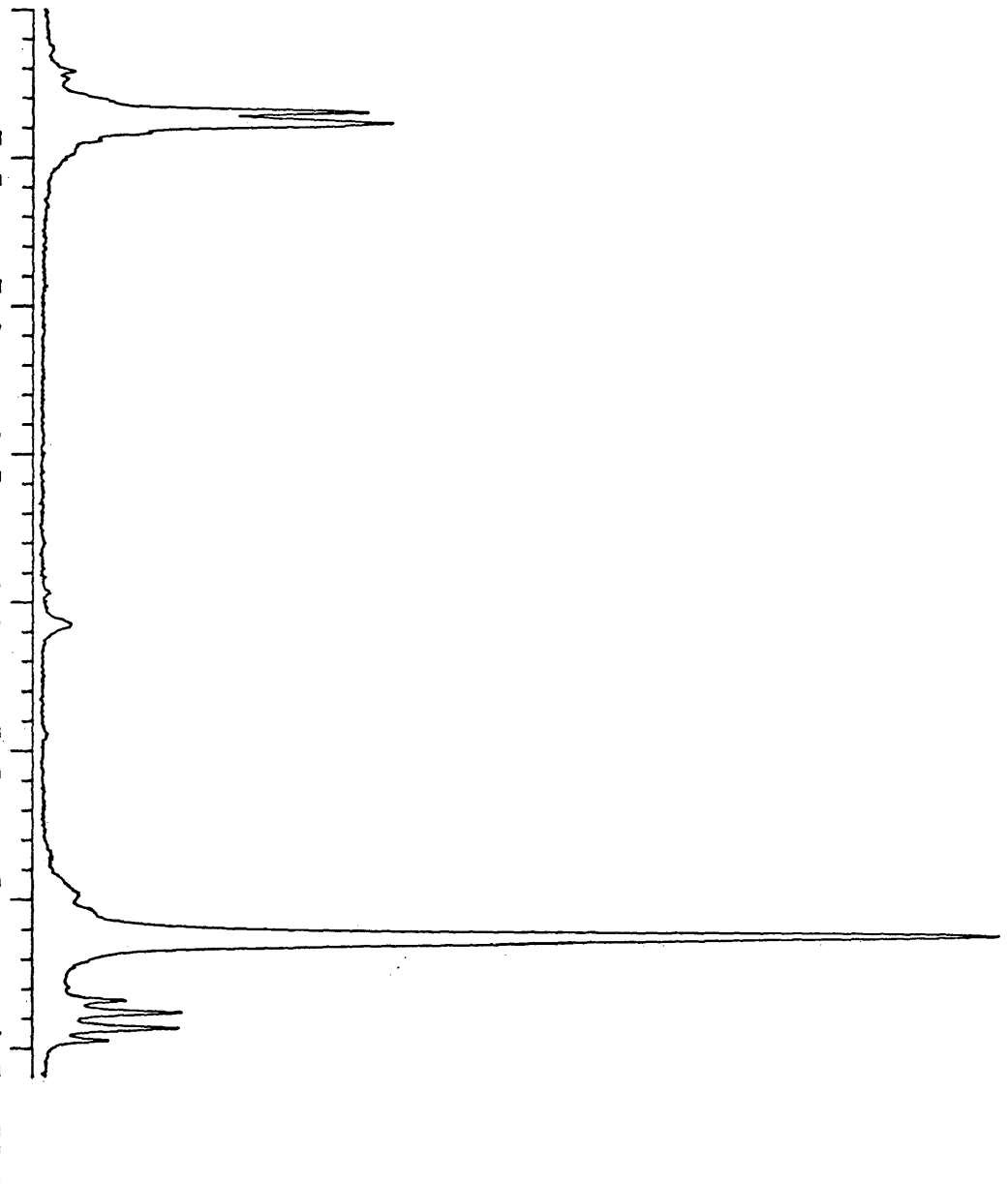


Fig. 32: ^{1}H NMR of meta C6 insertion product.

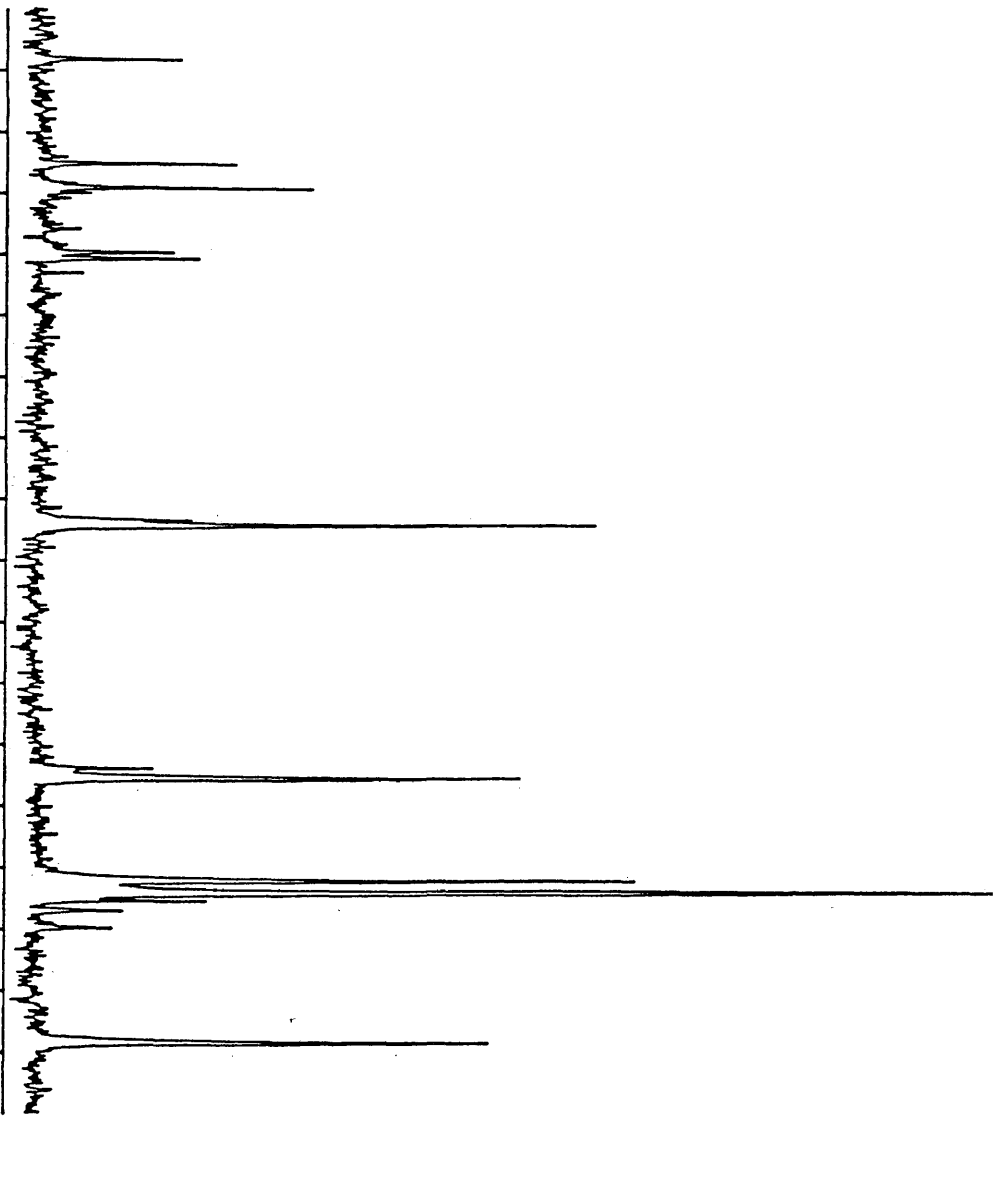


Fig. 33: ^{13}C NMR of meta C6 insertion product.

1. M. Bender and M. Komiyama, "Cyclodextrin Chemistry," Springer-Verlag: Berlin, 1978. p.2

2. K. Horikoshi, Process Biochemistry, May 1979, 26-30.

3. J. Pagington, Chemistry in Britain, May 1987, 455-458.

4. A. Stadler-Szoke and J. Szetjli, "Proc. First Int. Symp. Cyclodextrins," D. Reidel: Dordrecht, 1982. p. 377

5. J. Szejtli, "Proc. First Symp. Cyclodextrins," D. Reidel: Dordrecht, 1982. p. 467

6. J. Szejtli, "Cyclodextrin Technology," Kluwer Academic: Boston, 1988. p.80

7. I. Tabushi, Acc. Chem. Res., 15, 66-72(1982).

8. R. Breslow, Science, 218, 532-537(1982).

9. J. Szejtli, "Cyclodextrin Technology," Kluwer Academic: Boston, 1988. pp. 3-4

10. M. Bender and M. Komiyama, "Cyclodextrin Chemistry," Springer-Verlag: Berlin, 1978. p.3

11. R. Bergeron, J. Chem. Ed., 54, 4, 204-207(1977).

12. R.K. McMullan, W. Saenger, J. Fayos, and D. Mootz, Carbohyd. Res., 31, 37(1973).

13. W. Saenger, "Proc. First Int. Symp. Cyclodextrins," D. Reidel: Dordrecht, 1982. p. 141

14. J. Szejtli, "Cyclodextrin Technology," Kluwer Academic: Boston, 1988. p. 6

15. J.F. Wojcik and R.P. Rohrbach, J. Phys. Chem., 79, 2251(1975).

16. F. Cramer and F.M. Henglein, Angew. Chem., 68, 649(1956).

17. B. Siegel and R. Breslow, J. Amer. Chem. Soc., 97, 6869(1975).

18. J. Szejtli, "Cyclodextrin Technology," Kluwer Academic: Boston, 1988. p. 79

19. F. Cramer and F.M. Henglein, Chem. Ber., 90, 2561(1957).

20. J. Szejtli, "Cyclodextrin Technology," Kluwer Academic: Boston, 1988. p. 80

21. J. Szejtli, "Cyclodextrin Technology," Kluwer Academic: Boston, 1988. p. 84

22. F.M. Richards, Ann. Rev. Biochem., 32, 269(1963); W. Kauzmann, Adv. Protein Chem., 14, 1(1959); A. Wishnia and T.W. Pinder, Jr., Biochemistry, 5, 1534(1966).

23. A.D. Buckingham, Quart. Rev. Chem. Soc., 13, 183(1959).

24. F. London, Z. Phys., 63, 245(1930).

25. W. Saenger, Angew. Chem., 19, 344-362(1980).

26. J. Szejtli, "Cyclodextrin Technology," Kluwer Academic: Boston, 1988. pp. 87-90.

27. L. Szente and J. Szejtli, Herb. Hung., 19, 57(1980).

28. P.V. Demarco and A.L. Thakkar, Chem. Commun., 1970, 2.

29. P.V. Demarco and A.L. Thakkar, J. Pharm. Sci., 60, 652(1971).

30. J. Szejtli, "Cyclodextrin Technology," Kluwer Academic: Boston, 1988. pp. 132-133

31. R. Breslow and P. Cambell, Jour. of Amer. Chem. Soc., 91, 3085(1969).

32. J. Szejtli, "Cyclodextrin Technology," Kluwer Academic: Dordrecht, 1988. pp. 371-373.

33. D.E. Tutt and M.A. Schwartz, J. of Amer. Chem. Soc., 93, 767(1971).

34. R.L. VanEtten, J.F. Sebastian, G.A. Clowes, and M.L. Bender, Jour. of Amer. Chem. Soc., 89, 3242(1967).

35. R.L. VanEtten, J.F. Sebastian, G.A. Clowes, and M.L. Bender, Jour. of Amer. Chem. Soc., 89, 3253(1967).

36. M. Bender and M. Komiyama, "Cyclodextrin Chemistry," Springer-Verlag: Berlin, 1978. pp.34-41

37. W. Kirmse, "Carbene Chemistry," Vol. 1, Academic Press, New York, 1971. p.5

38. F. Carey and R. Sundberg, "Advanced Organic Chemistry," Part B, Plenum Press, New York, 1983. pp. 424-429

39. J.F. Harrison, Acc. Chem. Res., 7, 378(1974); R.K. Lengel and R.N. Zare, J. Amer. Chem. Soc., 100, 7495(1978); C.W. Bauschlicher, Jr. and I. Shavitt, J. Amer. Chem. Soc., 100, 739(1978).

40. G. Herzberg, Proc. Roy. Soc. London, Ser. A, 262, 291(1971).

41. G. Herzberg and J.W.C. Johns, J. Chem. Phys., 54, 2276(1971); J.A. Schellar, J. Chem. Phys., 58, 2882(1973).

42. N.C. Baird and K.F. Taylor, J. Amer. Chem. Soc., 100, 1333(1978).

43. J.F. Harrison, R.C. Liedtke, and J.F. Liebman, J. Amer. Chem. Soc., 101, 7162(1979).

44. M. Jones, Jr. and R.A. Moss, "Carbenes," John Wiley and Sons, New York, 1973. pp.153-304

45. M. Neeman and W.S. Johnson, Org. Synth., V, 245(1973).

46. L.I. Smith and K.L. Howard, Org. Synth., III, 351(1955).

47. W. Kirmse, "Carbene Chemistry," Vol.1, Academic Press, New York, 1971. p.29.

48. F. Carey and R. Sundberg, "Advanced Organic Chemistry," Part B, Plenum Press, New York, 1983. pp.430-431

49. C.S. Elliott and H.M. Frey, Trans. Faraday Soc., 64, 2352(1968).

50. F. Carey and R. Sundberg, "Advanced Organic Chemistry," Part B, Plenum Press, New York, 1983. pp. 435-441

51. B. Zurawski and W. Kutzelnigg, J. Amer. Chem. Soc., 100, 2654(1978).

52. H.E. Simmons and R.D. Smith, Jour. Amer. Chem. Soc., 80, 5323(1958); 81, 4256(1959).

53. J.H.-H. Chan and B. Rickborn, J. Amer. Chem. Soc., 90, 6406(1968); J.A. Staroscik and B. Rickborn, J. Org. Chem., 37, 738(1972).

54. R.C. Woodworth and S.K. Skells, J. Amer. Chem. Soc., 81, 3383(1958).

55. X. Creary, J. Amer. Chem. Soc., 102, 1611(1980).

56. A.M. Trozzolo, E. Wasserman, "Carbenes," Vol. II, Wiley: New York, 1975. pp. 185-206

57. J. Szejtli, "Cyclodextrin Technology," Kluwer Academic: Dordrecht, 1988. pp.154-159

VITA

Shelley Hunnings Smith

Born in Somerville, New Jersey, September 27, 1967. Graduated from Frank W. Cox High School in Virginia Beach, Virginia, June 1985. B.S. in Chemistry, The College of William and Mary, 1989. Summer Research Fellow, The College of William and Mary, Department of Chemistry, Summer 1988.

In June 1989, the author entered the College of William and Mary as a graduate student with a concentration of organic chemistry in the Department of Chemistry.

Upon completion of this thesis, the author plans to pursue a career in industrial chemical research with Rohm and Haas of Philadelphia, Pennsylvania.